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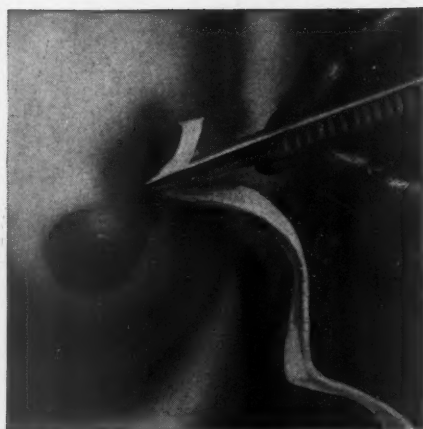
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THE AMERICAN SURGEON

Vol. 19, No. 11

November, 1953

STUDIES IN THE PRODUCTION OF EXPERIMENTAL MITRAL STENOSIS

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III, M.D., WILLIAM H. HEAD, JR., M.D., WILLIAM P. LONGMIRE, JR., M.D.

Los Angeles, Calif.

For many years efforts have been made to produce mitral stenosis in the experimental animal. The problem has been attacked with renewed vigor since the development of procedures for the relief of mitral stenosis in patients. In this paper we are reporting our experiences in attempting to produce this valvular deformity in experimental animals.

The first successful production of some degree of constriction of the mitral valve was accomplished in 1 animal in 1909 by Bernheim,¹ who placed an encircling ligature about the mitral ring. Cutler, Levine, and Beck⁶ used a variety of methods but were unsuccessful in producing significant mitral stenosis. Coryllos, Edwards, and Bagg⁵ irradiated the valve through the left auricular appendage but succeeded only in producing large scars. Powers,^{11, 12} first cauterized the valve leaflets then injected cultures of streptococci into the blood stream in an attempt to produce vegetations upon the traumatized valves. Actual significant valvular stenosis with pulmonary hypertension failed to appear. Wilson¹⁵ created obstruction at the mitral orifice by passing cords of pericardium through the ventricular wall so that they lay across the valve opening. Again, while some degree of obstruction was produced at the mitral orifice, the degree of stenosis was not significant. Shaw and co-workers¹⁴ attempted to produce mitral stenosis by temporarily occluding the superior and inferior venae cavae and then either suturing the valve leaflets together or encircling the chordae tendinae with a ligature. Significant signs of cardiac decompensation did not develop in any of these animals. Connolly⁴ has produced some degree of stenosis by using an encircling ligature about the valve

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ring, and Clowes^{2, 3} recently used an extracorporeal pump to by-pass the left side of the heart in order to approximate the leaflets of the exposed mitral valve with sutures under direct vision. Valvular stenosis was thought, in most instances, to be progressive. Ferrin, Adams, and Baronofsky⁴ used a number of methods in an attempt to produce mitral stenosis, the most satisfactory of which was to pass two mattress sutures of silk across the mitral ring and tie them over buttons. They believed that this method consistently produced elevated pressures in the pulmonary veins.

One of the simplest and most effective methods is that used by Ellison and associates.⁷ It consists of passing a steel wire, which has been threaded into nylon tubing about the base of the valve and passing the ends through a cannula fixed to the wall of the chest so that the ligature can be gradually tightened over a period of time.

METHODS AND RESULTS

Administration of Desoxycorticosterone (DOCA) and Production of Arteriovenous Fistulas. Based upon the hypothesis of Selye,¹³ concerning the process of repair when inflammation and scarring play an important role and the reports of Lillehei and co-workers¹⁹ and Gowdy and co-workers,⁹ large arteriovenous fistulas were produced in 15 dogs. All of these dogs were given 15 mg. of desoxycorticosterone* daily for a period of one week. At this time a unilateral nephrectomy was done in order to enhance the effect of the drug, and a large arteriovenous fistula was created between the aorta and vena cava or between the common iliac artery and vein. A high mortality rate was encountered in attempting to produce large arteriovenous fistulas. Those larger than 4 or 5 mm. in diameter between the aorta and inferior vena cava proved fatal to most of the animals within from 24 to 72 hours. Those produced between the common iliac artery and vein likewise resulted in a high mortality rate. In the latter group there was a high incidence of edema and gangrene of the extremity involved. Ten of the dogs died within two weeks after operation. The 5 remaining dogs were given desoxycorticosterone daily for an additional 15 days. The fistula in each of these dogs was approximately 5 mm. in diameter. Additional trauma to the mitral valve was done in 3 of these animals by exposing the left auricle through a thoracotomy and passing a glass rod with carborundum cloth attached to one end through the left auricular appendage and abraiding the mitral valve. Marked generalized edema and cardiac hypertrophy had developed in 2 of the dogs, and they died during the attempt to abraid the valve. One animal, in which the operation was successfully accomplished, was killed after four months, and only slight edema and slight thickening of the valve were present. One of the remaining animals died in heart failure three and one-half months after operation, and the other was killed seven months after the arteriovenous fistula had been produced, and only edema and thickening of the valve were noted.

Inversion of the Left Auricular Appendage through the Mitral Valve. Another

* The desoxycorticosterone was kindly furnished by Walter N. Holmstrom of CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

way in which we attempted to produce mitral stenosis was to invert the left auricular appendage through the mitral valve orifice and suture it to the wall of the left ventricle. It was thought that this might cause narrowing of the mitral valve in two ways. First, the actual presence of the appendage in the mitral orifice might produce enough impediment to blood flow to cause pulmonary hypertension. Second, the repeated striking of the leaflets against the wall of the appendage might cause enough trauma to the leaflets to create some scarring and stenosis.

In order to invert the auricular appendage, it was first exposed through incisions in the left fifth intercostal space and pericardium. A suture was then secured in the tip of the appendage, and by using a long curved needle the end of the suture was passed into the auricle, through the mitral valve, and out of the wall of the left ventricle (fig. 1A). By drawing this end taut and fixing it to the ventricular wall, the appendage could be invaginated through the valve and maintained in that position (fig. 1B).

This procedure was done in a series of 13 rabbits and 5 dogs. It was accompanied by an immediate high mortality rate in the rabbits. This was due to intolerance of the rabbit's heart to manipulation. Five survived the immediate postoperative period. Autopsies were done on these animals from four to seven months after operation and showed evidence of valvular scarring and pulmonary hypertension in only 1 animal. In this animal pink frothy sputum and bright red bleeding from the nose suddenly appeared four months after operation, and death occurred shortly after these signs were noted. Autopsy revealed areas of thickening and nodularity on the mitral valve adjacent to the inverted auricular appendage. The lungs showed slight edema.

Five dogs were operated upon by the procedure described above. In addition, a sheet of reactive cellophane was sutured onto the endocardial wall of the appendage. This was done by placing a clamp across the base of the appendage and inserting the cellophane through an opening in the distal portion. When the appendage was inverted, the cellophane came in contact with the valve, and it was thought that this reactive material might cause further trauma and scarring of the leaflets.

Two of the dogs died during the procedure. One was killed at four months and showed slight thickening of the free edges of the valve leaflets. The other 2 were killed at six and seven months respectively and showed that the appendage partially occluded the valve opening. Slight nodularity of the valve leaflets was present. Cardiac catheterization before the animals were killed revealed elevated right ventricular and pulmonary artery pressures (table I).

Injection of Reactive Material about the Valve Ring. Another method was one which was designed to produce chronic inflammation and scarring of the valve ring. This involved the injection of a material into the valve ring which would chronically irritate it and produce scarring and cicatrization. The agents used were radioactive chromic phosphate* and dicetyl phosphate.† An incision was

* The radioactive chromic phosphate was furnished by Donalee L. Tabern of Abbott Laboratories, North Chicago, Illinois.

† The dicetyl phosphate was furnished by Paul Logue of the Monsanto Chemical Company, St. Louis, Missouri.

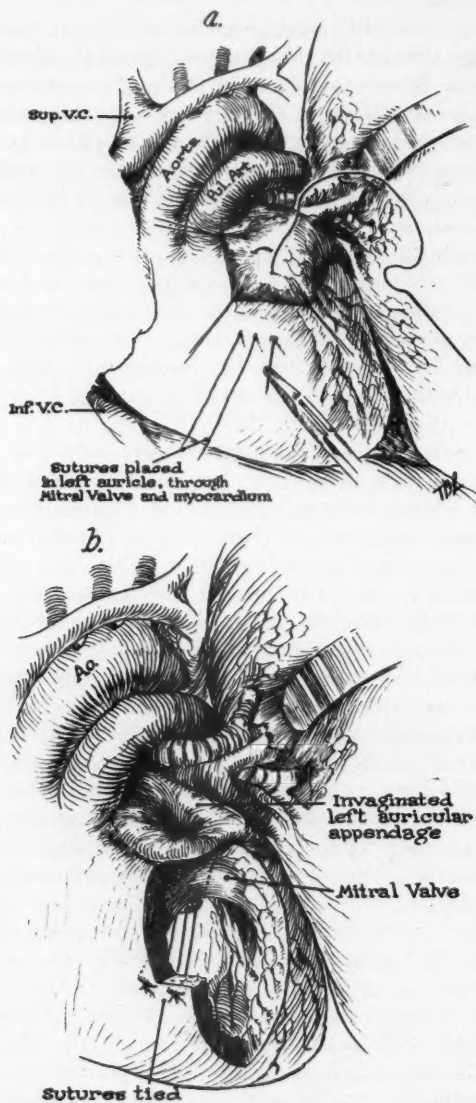


FIG. 1. (A) Sutures have been placed in the apex of the left auricular appendage and passed through the valve and out through the myocardium of the left ventricle. (B) The previously placed sutures have been pulled taut, invaginating the left auricular appendage through the mitral valve and thus partially obstructing the valve.

made in the left fifth intercostal space. Through openings in the mediastinal pleura, the superior and inferior venae cavae were mobilized and tapes were passed about them. The left auricular appendage was exposed through an

incision in the pericardium and the venae cavae were then occluded by the tapes. The left auricular appendage was opened and the mitral valve was exposed. The reactive material was injected into the valve ring in 0.1 cc. amounts at intervals of about 5 mm. (fig. 2). The venae cavae were released and the auricle was allowed to fill with blood to prevent air embolism in the coronary

TABLE I
Auricular inversion with cellophane on auricular wall

Dog	Postoperative Course	Catheterization				Autopsy
		Time Postoperative	R. Aur.	R. Vent.	Pul. Art.	
1	Died on table	Not catheterized				4 mo.—slight thickening of free edges of cusps
2	—					
3	Died on table	6 mo.	12/2	60/4	60/14	6 mo.—appendage well inverted—slight nodularity of valve
4	—					
5	—	7 mo.	16/-6	76/4	78/16	7 mo.—appendage well inverted—same

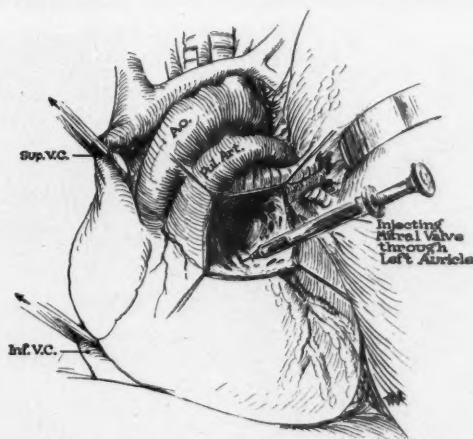


FIG. 2. The venae cavae have been temporarily occluded and the left auricular appendage opened wide. Radioactive material is being injected about the circumference of the valve ring.

arteries. A Potts ductus clamp was placed across the left auricular appendage and the incision in the appendage was closed. The pericardium and chest were closed with silk sutures. The venae cavae were usually occluded for from two to three minutes. Adrenalin was occasionally necessary to aid in initiating cardiac contractions.

In 9 dogs 1 cc. of a solution containing approximately 1 mc. of radioactive

chromic phosphate was injected about the ring. One animal died during the procedure. One died 48 hours after operation and postmortem examination revealed an inflamed hemorrhagic area on the anterior myocardial wall in the region of the left coronary artery. Another died 10 days after operation and showed only scattered areas of necrosis about the valve ring. One was killed 6 weeks after operation and examination revealed similar findings. Four were killed from four to five months after operation and 1 eight months after operation. Gross examination showed a normal valve in all of these animals. Cardiac

TABLE II
Reactive material injected about valve ring

Dog	Postoperative Course	Cardiac Catheterization Time postoperative	Autopsy Time postoperative
<i>P-32 Chromic Phosphate</i>			
1	Survived	Not catheterized	6 wk.—scattered areas of necrosis about valve ring
2	Survived	4½ mo.—normal pressures	Normal valve
3	Survived	3½ mo.—normal pressures	Normal valve
4	Died 10 days po.	Not catheterized	10 days —scattered areas of necrosis about valve ring
5	Survived	4 mo.—normal pressures	Normal valve
6	Died during op.		
7	Died 48 hrs. po.		48 hr.—hemorrhagic area on anterior myocardial wall near left coronary artery
8	Litter of 9 normal pups 6 mo. po.	8 mo.—normal pressures	Normal valve
9	Survived	4 mo.—normal pressures	4 mo.—normal valve
<i>Dicetyl Phosphate</i>			
10	Survived	Not catheterized	1 mo.—normal valve
11	Died during op.		
12	Died 1 day po.		
13	Died 18 days po.	Not catheterized	18 days—large necrotic area in wall of rt. ventricle
14	Survived	3 mo.—normal pressures	3 mo.—normal valve
15	Died 1 day po.		

catheterization was done before the animals were killed and revealed normal right ventricular and pulmonary artery pressures.

In 6 additional dogs 1 to 2 cc. of a 2 per cent solution of dicetyl phosphate was injected into the valve ring. Three died in the early postoperative period, and 1 died of infection 18 days after operation. One was killed one month after operation and 1 at three months after operation. The mitral valve in both of these animals appeared to be normal. Cardiac catheterization revealed no elevation of the right ventricular or pulmonary artery pressure in the dog killed three months after operation (table II).

Obstruction and Chronic Trauma to the Valve by Object placed through Valve Opening. Another approach which was used involved placing an object in the valve opening and fixing it so that it would remain in that position. It seemed possible that the constant trauma to the valve leaflets and the reaction about

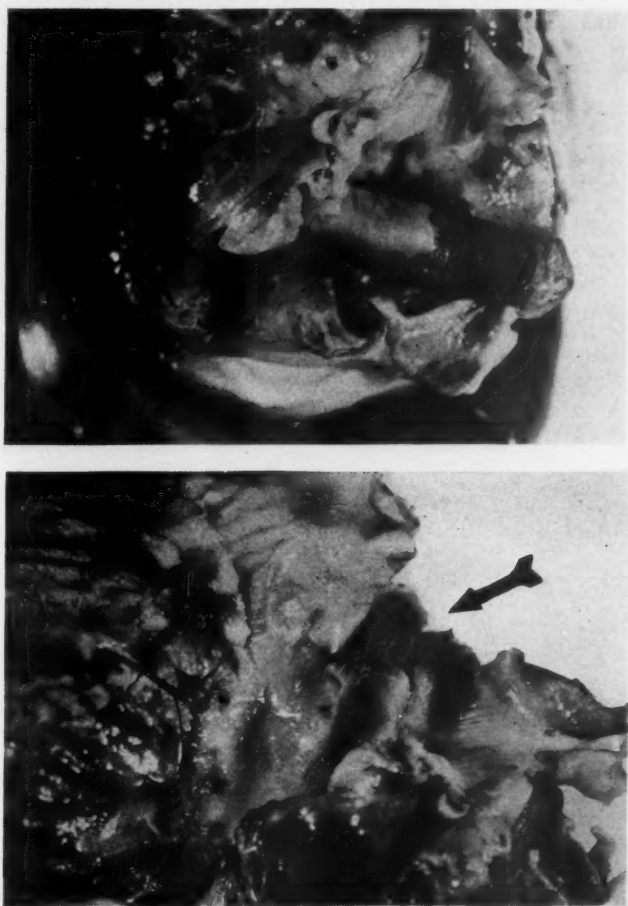


FIG. 3. Photographs of specimen taken at autopsy showing reaction about the polyethylene tube seven months after it was placed through the mitral valve and fixed in position. The lower end is covered with a sheath of fibrous tissue and is densely adherent to the valve leaflet.

such an object might cause narrowing of the valve opening. Therefore, the left auricular appendage was exposed through incisions in the left fifth intercostal space and the pericardium. A 2 in. length of $\frac{1}{4}$ in. polyethylene tubing, both ends of which were sealed, was passed through the left auricular append-

age into the mitral valve opening, and one end was sutured to the midportion of the left auricular appendage. The incisions in the pericardium and thorax were closed. This procedure was done on 3 dogs. One died one month after operation and showed local scarring of the valve leaflets where they had come in contact with the tube. Another died two months after operation, and the tube was found to have migrated through the mitral valve and had eroded

TABLE III
Polyethylene tube through mitral valve

Dog	Course	Cardiac Catheterization				Autopsy
		Time postoperative	R. Aur.	R. Vent.	Pul. Art.	
1	Died 1 mo. po.	Not catheterized				Reaction about tube Tube migrated through valve and eroded aortic cusp
2	Died 2 mo. po.	Not catheterized				
3	Killed 7 mo. po.	7 mo.	22/14	44/20	46/34	Marked reaction of valve leaflets near tube—tube covered with fibrous sheath

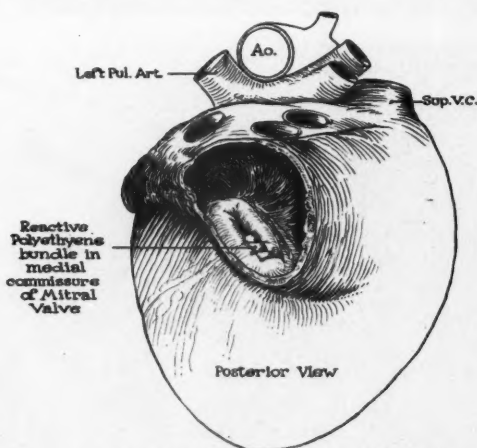


FIG. 4. A bundle of reactive polyethylene film has been placed in the medial commissure of the mitral valve, and the sutures which were passed through the leaflets have been tied over it.

one of the aortic valve cusps. One animal was killed seven months after operation and showed only thickening of the valve and scarring about the tube (fig. 3A and B). Catheterization of this animal showed increased right ventricular and pulmonary artery pressures (table III).

Direct Suture Together of Valve Leaflets over Reactive Polyethylene Bundle. In 4 dogs the valve was exposed through an incision in the left auricular appendage by the same method that we used for injection of reactive substances into the

valve ring. A suture was passed through the edges of the valve leaflets about one-third of the distance from the annulus and tied over a small bundle of reactive polyethylene film* (fig. 4). Two animals died in the immediate postoperative period. About three months after operation 1 of the animals showed signs typical of cardiac failure, including peripheral edema, ascites, and frothy

TABLE IV
Suture together of valve leaflets over polyethylene bundle

Dog	Course	Cardiac Catheterization				Autopsy Time postoperative
		Time postoperative	R. Aur.	R. Vent.	Pul. Art.	
1	Died during op.					
2	Died 1 day po.					
3	Cardiac failure 3 mo. po.	4 mo.	21/-2	66/-3	Not entered	4 mo.—advanced stenosis marked reaction about polyethylene bundle
4	Survived	4 mo.	12/8	36/2	30/20	4 mo.—moderate stenosis, marked reaction about polyethylene bundle

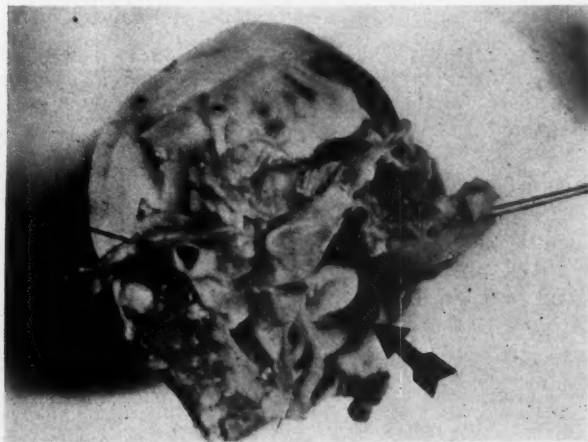


FIG. 5. Photograph showing mitral valve five months after the leaflets were sutured together over a bundle of reactive polyethylene film. There is marked tissue reaction about the polyethylene bundle. Advanced mitral stenosis is present.

sputum. These signs were alleviated by the administration of digitalis. Cardiac catheterization done four months after operation showed that the right ventricular pressure was 66/-3 and the right auricular pressure was 21/-2. The

* The reactive polyethylene, Type NV-7-14, was furnished by W. M. Ryan of E. I. du Pont de Nemours and Company, Wilmington 98, Delaware.

catheter could not be inserted into the pulmonary artery. Autopsy following catheterization revealed advanced stenosis with thickening of the valve leaflets about the reactive polyethylene (fig. 5). The other animal showed no signs of cardiac failure. Catheterization four months after operation revealed a right ventricular pressure of 36/2, pulmonary artery pressure of 30/20 and right auricular pressure of 12/8 (table IV).

DISCUSSION

One can see from the problems encountered by previous investigators and by us that to produce valvular stenosis similar to that found in rheumatic heart disease is indeed difficult. When great narrowing of the mitral orifice is acutely produced, cardiac arrest results in a high number of instances and is probably caused by a combination of factors, the chief of which are decreased coronary artery blood flow and right ventricular failure. Extensive trauma to the mitral valve with or without the production of vegetative endocarditis usually results in marked destruction of the valve.

Theoretically it should be possible to inflict some form of trauma upon the mitral valve and produce a constricting scar that would closely simulate mitral stenosis found in patients with rheumatic heart disease. However, it should be borne in mind that mitral stenosis caused by rheumatic heart disease in patients is a result of a so-called verrucous or proliferative endocarditis as contrasted to the vegetative or destructive form of endocarditis. The vegetative form is usually seen in various types of bacterial endocarditis in patients and is characterized by large masses of vegetations loosely attached to the mitral valve. These vegetations may break loose in the circulatory system resulting in bouts of embolism. In this type of endocarditis, the reparative process is not as rapid as the destructive process, and thus necrosis of the valve leaflets occurs.

Clinical bacterial endocarditis does not usually result in mitral stenosis of appreciable degree. On the contrary, mitral insufficiency often ensues. Verrucous endocarditis, on the other hand, occurs in rheumatic heart disease and is characterized by a slow inflammatory process. In this instance repair exceeds destruction so that over a period of time heaping up of collagen and connective tissue on the valve leaflets may frequently result in thickening and scarring and subsequent stenosis. Insufficiency of various degrees may accompany the stenosis but is usually only minimal or moderate.

Generally speaking, our methods have involved three principles in attempting to produce mitral stenosis. The first was to try to produce endocarditis by administering DOCA and producing large arteriovenous fistulas. This method appears to be of no value in producing mitral stenosis. Our animals did not develop extensive endocarditis; and while nodularity and edema were noted chiefly in the mitral valve, they were also present to a lesser extent in the other heart valves. Therefore, even if significant stenosis could be produced by this method, it would probably not be limited to the mitral valve.

The second principle was to try to produce an extensive cicatrizing reaction in the valve, either by traumatic or chemical irritation. We used radioactive

chromic phosphate and dicetyl phosphate, injecting them directly into the valve ring to try to produce a chronic reaction in it. If a large quantity of radioactive material is injected into the ring, necrosis and sloughing occur. Also, Coryllos, Edwards, and Bagg⁵ have demonstrated that very large single doses of irradiation to the valve leaflets result in necrosis and sloughing of the leaflets. The same may be said for the dicetyl phosphate. The quantities which we used were well tolerated and the scarring that resulted was insignificant. It seems, therefore, unwise to pursue this method further.

Passing the 2-in. length of $\frac{1}{4}$ in. polyethylene tube through the mitral valve and allowing it to remain in this position resulted in considerable inflammatory reaction in the valve so that the polyethylene tube was enveloped in a dense sheath of connective tissue on one of the leaflets. While we did not continue this approach, it seems possible that by using polyethylene tubing of a larger caliber, stenosis might be produced by the partial occlusion of the valve opening by the tube as well as by the considerable inflammatory reaction in the valve leaflets about the tube.

The third principle employed mechanical obstruction of the valve, and it was attempted in two ways. First, the auricular appendage was inverted through the valve opening and sutured to the ventricular wall. This method resulted in pulmonary hypertension in 2 of 3 of the animals who survived the operation. One problem encountered in the technic of this procedure was the determination of the proper degree to which the appendage should be inverted. Some information in this regard might be obtained by measuring the pulmonary venous pressure before the appendage is inverted and noting the rise in pressure over a period of from 15 to 30 minutes after it has been inverted. Otherwise, the method appears to be relatively simple and may be of practical value in producing physiologic mitral stenosis.

Suturing the valve leaflets partially together over a bundle of reactive polyethylene film also resulted in mitral stenosis. This procedure is most easily accomplished by means of a left heart pump which Clowes has used, but it may also be accomplished by temporarily arresting the venae cavae as Shaw had done previously and as we did in order to suture the leaflets under direct vision. The obvious disadvantage of vena caval occlusion is that one is limited by the short period of time that the circulation can be arrested. Therefore, the valve leaflets cannot be as accurately approximated as when the left heart pump is used. Direct suturing of the valve leaflets together or the method used by Ellison and associates would seem to be the most satisfactory method for producing experimental mitral stenosis at the present time. Care should be taken not to occlude the valve opening to too great an extent. The incorporation of the bundle of reactive polyethylene film causes an inflammatory reaction in the valve leaflets so that the stenosis is progressive. When one uses a method which requires opening the left side of the heart, cardiac arrest from air embolism in the coronary arteries is likely to occur unless one is sure that the left ventricle and auricle are filled with blood or saline solution before closing the incision in the auricle.

From the standpoint of devising a procedure for mitral valvulotomy in pa-

tients, the value of a practical method for producing experimental mitral stenosis does not seem as paramount as it did several years ago, because a successful method to relieve mitral stenosis in patients has been developed. However, a practical experimental method for producing mitral stenosis might offer an opportunity to study the development of changes in hemodynamics of the pulmonary circulation and the development and nature of pulmonary vascular changes which result from long standing pulmonary hypertension as well as in determining criteria for operability and the prognosis of patients undergoing mitral valvulotomy.

SUMMARY

The development of a satisfactory procedure for the surgical relief of mitral stenosis in patients has stimulated interest in the development of a practical method to produce the deformity in laboratory animals.

Investigations reported previously in the literature on this problem are reviewed.

Methods which we have used in attempting to produce mitral stenosis in dogs include the creation of large arteriovenous fistulas with additional trauma by abraiding the valve, inversion of the auricular appendage through the valve, injection of radioactive chromic phosphate and dicetyl phosphate into the valve ring, suturing an object in the valve opening, and suturing the valve leaflets together over a bundle of reactive polyethylene film.

Physiologic mitral stenosis was produced in 2 of the animals by inversion of the auricular appendage. Advanced stenosis was produced in 1 dog and moderate stenosis in another by suturing the valve leaflets together over a bundle of reactive polyethylene film.

The advantages and disadvantages as well as possible further application of the methods used are discussed.

The authors wish to acknowledge the technical assistance of Paul E. Johnson, Jr.

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CANCER OF THE THYROID—A REVIEW OF FORTY-SEVEN CASES

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In the seven and one-half year period from July 1945 through December 1952, 47 consecutive cases of carcinoma of the thyroid gland were treated at St. Thomas Hospital. Only those cases submitted to pathologic study were selected for inclusion in this series. Of 1253 operations up on the thyroid gland during this period the incidence of malignancy was 3.7 per cent.

McSwain and Diveley²² report that malignant tumors of the thyroid gland are uncommon in a general hospital which is located outside of the goiter belt. They reported a total of only 23 patients over a 22 year period. This is at variance with the incidence in the present series. This discrepancy exists despite the fact that both series were reported from hospitals in the same city, both admitting patients from essentially the same locale.

It has been stated that malignant tumors of the thyroid gland comprise about 1 per cent of all human cancer.^{29, 10} Beahrs and Judd³ have stated that it is not possible to determine the exact incidence of carcinoma of the thyroid gland, since large segments of the population have not been studied. Much of the data in the literature concerns itself with the incidence of association with goiter. Reports based upon autopsy studies and including all types of goiter have appeared, which ostensibly show that cancer of the thyroid is a rare disease and that there is little indication for removing a small nodule in the thyroid because of the danger of malignant degeneration.² However, others have pointed out that the number of cases in which the cause of death is reported in the autopsy records of a large hospital as cancer of the thyroid, is an inaccurate estimate of the number of patients who actually succumb to this disease.⁸ Most of these patients die at home and many are never seen again at that particular institution.

It has been stressed by several investigators that the incidence of carcinoma is significantly greater in non-toxic goiters with a solitary nodule than in goiters with multiple nodules. In establishing a standard for nodularity, the combined descriptions by the surgeon and the surgical pathologist were used as a basis for assessing nodularity. Since lobectomy or partial thyroidectomy was generally used in the operative treatment in this series, the error in this method appears reasonably small.

Three hundred nineteen patients presenting the impression of non-toxic goiter with a solitary nodule were operated upon. Carcinoma was found in 30 of this group or 9.4 per cent. Non-toxic multinodular goiters were found in 280 patients and of these 15 were found to have carcinoma, an incidence of 5.3 per cent. One case of carcinoma was encountered in association with chronic thyroiditis and one undifferentiated carcinoma was found within a nodule occurring

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in a patient with a diffuse toxic goiter. This last finding seems in keeping with the extremely low incidence of malignancy of the thyroid associated with hyperthyroidism as reported by numerous observers.^{18, 12} Crile and Fisher¹³ have recently reported on the simultaneous occurrence of thyroiditis and carcinoma.

Table I is illustrative of the 1253 cases studied in this series from the standpoint of pathology involved, age range and sex.

Table II is illustrative of the distribution of thyroid carcinoma and non-toxic nodular goiters. The observation of Ward, Cole and others that the relative incidence of carcinoma in non-toxic nodular goiters is greater in men than in women has not been borne out in this series.^{20, 9, 27} Reports from various clinics have shown considerable variation in the incidence of malignancy in discrete nodules of the thyroid. For example, Cole reports 24 per cent, Crile 24 per cent,

TABLE I

Pathology	No. of Cases	Age Range	Male	Female
Carcinoma.....	47	7 to 75	5	42
Toxic diffuse goiter.....	383	10 to 78	53	330
Toxic nodular goiter.....	141	21 to 73	11	130
Non-toxic diffuse goiter.....	39	28 to 60	3	36
Non-toxic nodular goiter.....	599	7 to 78	45	554
Chronic thyroiditis.....	44	10 to 72	2	42

TABLE II

Pathology	No. of Cases		No. of Carcinoma		Per cent Carcinoma
	Male	Female	Male	Female	
All non toxic nodular goiters.....	45	554	5	42	7.8

Ward 15 per cent, and Lahey 10 per cent. Our incidence of 9.4 per cent is somewhat lower than the above averages.

Malignancy incidence in children has been reportedly much higher than in adults. For example, Kennedy,¹⁹ in a study of non-toxic nodular goiters in a group of children under 15 years of age found malignant degeneration in 12 out of 27, an incidence of 44 per cent.

The malignant tumors in this series have been placed in the following categories with their relative incidence and patient age as depicted in table III.

Papillary adenocarcinoma comprises the largest histologic group reported in all large series of thyroid carcinoma reviewed.^{3, 16, 20, 14, 10} Relative incidences indicate that about one-half of all malignancies of the thyroid are papillary in type.

It is now generally accepted that the majority of all cancers of the thyroid arise in pre-existing adenomas and there seems to be little question of the wisdom of advising prompt removal of discrete adenomas.^{20, 27, 16, 23, 20, 6, 8, 24, 9, 29} This

same conclusion is reached even if one believes, as Crile does¹⁹, that a malignant nodule in the thyroid does not arise in a pre-existing benign adenoma but has been a malignant adenoma from the beginning, although its size has not varied for months or years. Crile has stated that carcinoma of the thyroid in almost every instance first manifests itself as a discrete nodule in one lobe of the thyroid gland and that the incidence of carcinoma in these solitary tumors is so high that they should all be removed.

The problems encountered in the surgical treatment in cases of nodular non-toxic goiter merit special emphasis. Operations for this disease should remove the goiter, alleviate symptoms related to its presence, assure as well as possible against its recurrence, and provide adequate local treatment should an unsuspected neoplasm be present. At the same time the morbidity rate should be low, and sufficient glandular tissue should be left in place to prevent postoperative myxedema.

TABLE III

Pathology	No. of Cases	Per cent of Total No. of Malignancies	Age Range	Average Age of Patients
A. Low to moderate grade malignancy				
Invasive adenoma	7	14.9	27 to 51	39
Hurthle cell carcinoma	4	8.5	42 to 75	59
Papillary adenocarcinoma	24	51.2	14 to 70	37
Alveolar carcinoma	2	4.2	7 to 71	39
Adenocarcinoma	3	6.4	9 to 66	28
B. High grade malignancy				
Anaplastic carcinoma	2	4.2	40 to 46	43
Giant cell carcinoma	2	4.2	55 to 67	61
Unclassified	3	6.4	44 to 66	56

The problem of how to deal with unsuspected carcinoma in nodular goiter seems particularly important. Review of these cases indicates that carcinoma is usually not recognized at the time of operation unless there is evidence of extension to surrounding structures or metastases are present. A preoperative clinical diagnosis of suspected malignancy was made in 16 of the 47 cases, an incidence of 34 per cent. Reported accuracy of preoperative diagnosis varies from 6.8 per cent to 90 per cent.

Branson (London)	6.8%
Clute (Boston)	67.0%
Pemberton (Rochester)	40.0%
Cole (Chicago)	75.0%
Crile (Cleveland)	90.0%. ^{9, 21}

Since simple enucleation of the adenoma and partial removal of a lobe are inadequate in cases in which unsuspected carcinoma is present,⁹ it would seem

that lobectomy should be advocated in the treatment of these cases. One should think of discrete tumors of the thyroid not as benign adenomas which may become malignant at some time but rather as tumors which may be cancerous at the time of operation.^{12, 20}

Lobectomy, including the isthmus, best answers the criteria stated above and at times provides all the operative intervention required if carcinoma is discovered in the specimen.^{21, 22} If lobectomy is not the routine practice of the surgeon, it would seem essential that the diagnosis be established correctly before operation so that adequate surgery can be done.¹⁰

Attempts to devise a standardized surgical procedure for managing carcinoma of the thyroid gland have not been signally successful, chiefly because of the marked differences in biologic behavior of the different types of carcinoma. Thus, a procedure that seems rational for the management of papillary lesions may be irrational for the treatment of malignant adenomas or giant cell carcinoma.^{29, 5}

Goiters which are obviously highly malignant and rapidly growing present their own problems and these are generally concerned with the complications and management of terminal care. Surgery has little to offer for highly malignant goiters and if attempted, may lead to greater difficulties or actually to disaster.²⁷ Fortunately, these tumors comprise a small portion of the total.

The usual natural history of the less malignant neoplasms is characterized by long periods of either complete growth inactivity or of extremely slow growth, followed by periods of relatively rapid growth, and eventually by widespread dissemination.^{27, 15, 16}

Neoplasms may appear in distant foci years after the primary focus in the neck has been removed or years after evidence of growth has ceased at the primary site.¹ These tumors may spread by a number of routes; lymphatic, venous and direct invasion. The commonest spread is a contiguous invasion of surrounding structures. The prethyroid muscles, particularly the sternothyroid muscle, are frequently involved. Direct spread may occur to the carotid sheath and its contents, but particularly, direct invasion may occur through the middle thyroid vein to the jugular vein. The trachea and esophagus may be directly involved and extension may occur into the upper mediastinum, and subpectoral areas. Spread through the lymphatics to the deep chain of cervical nodes with later involvement of the more superficial nodes is common.^{7, 1, 20, 16, 23} The papillary types follow a pattern characterized by a tendency to local recurrence, regional lymph node involvement and lung metastases.

The natural history of this form of carcinoma is characterized by long periods of survival with repeated recurrences in cervical lymph nodes.²¹ The malignant adenoma often does not recur locally even after simple enucleation; does not involve the regional lymph nodes; metastasizes early to bone, and apparently only late to the lung.¹⁵ Blood vessel invasion within the primary tumor is a frequent finding.²⁰ It occurred in this series in 32 per cent of the patients.

There has been no clear cut accepted indication for the use of neck dissection. Survival and recurrence rates have been disappointing in the evaluation of

the procedures which have been proposed, partly because of the slow natural progress of lower grades of malignancy and partly because of extremely rapid progress of more malignant lesions.⁵

Crile^{11, 10} has suggested that local excision of nodules lateral to the jugular vein or sternocleidomastoid muscle may be sufficient for control, and states that reported results of conservative operations on the lateral cervical metastases are as good or better than reported results of block dissection and roentgenotherapy. His belief is that although block dissection of the neck may be valuable in the treatment of recurrent cancer, it is not necessarily the proper treatment for the primary manifestations of the disease.

In general, Black^{5, 4} of the Mayo Clinic believes that removal of the anatomic group or groups of nodes in which metastatic growth has developed is sufficiently radical. This view is based upon the fact that malignant adenomas and diffuse adenocarcinomas almost invariably prove inoperable by the time sufficient spread has occurred to involve adjacent structures.¹⁷ On the other hand, surgeons

TABLE IV

Pathological Type	Total No. of Cases	Block Neck Dissection	Rec. Postoperative Roentgen Ray Treatment
Invasive adenoma	7	0	1*
Papillary adenocarcinoma	24	4	12
Alveolar carcinoma	2	0	2
Adenocarcinoma	3	0	3
Hurthle cell carcinoma	4	0	1
Anaplastic carcinoma	2	0	2
Giant cell carcinoma	2	0	2
Unclassified	3	0	3

* Given as adjunct treatment in pathological fracture of the femur occurring two years following excision of thyroid malignancy.

such as Cole⁹, Ward²⁹, Cattell⁷, Lahey²⁰, and Frazell¹⁶ believe that local excision of nodes does not seem reasonable and that if surgery is to be used in an effort to effect permanent cure, it must be designed to remove all tumor-bearing tissue.

Moreover, reports of large numbers of patients have appeared in which neck dissection has been done revealing malignant involvement of the cervical nodes in as high as 88 per cent of the cases.^{7, 14, 5, 16} The inadequacy of partial lobectomy in the management of even papillary lesions has been demonstrated by Black.⁴ He reports that in 36 cases of papillary adenocarcinoma in which partial lobectomy had been done, there was recurrence in the remnant in 4 cases.

In the 47 cases herein reviewed palpable cervical nodes were clinically present in 11 cases. Radical block dissection of the neck was undertaken in 4 cases, all for papillary adenocarcinoma, and postoperative deep roentgen ray treatment was given in 25 of the cases. Table IV depicts pathological type and cases receiving block neck dissection and post-operative roentgen ray treatment.

Irradiation has proved to be a useful adjunct to the treatment of thyroid carcinoma,²⁹ and is used routinely by some clinics.^{7, 14, 27} However, others^{10, 16} believe that the value of postoperative roentgenotherapy has been over emphasized.

The therapeutic efficacy of I^{132} depends upon the ability of the tumor or its metastases to take up the iodine. It has been shown that, following total removal of the thyroid, metastases, if present, may take on thyroid function to a considerable degree.²⁹ Some may be made to do so by giving thyroid stimulating hormone or propylthiouracil to induce function in the metastases.²⁶ Well differentiated follicular carcinoma and malignant adenomas have the greatest ability to assimilate and hold iodine, their metastases showing the same ability. The less differentiated malignancies and their metastases lack the capacity to concentrate iodine and are therefore not amenable to effective treatment with this radioactive isotope.^{15, 28, 25}

SUMMARY AND CONCLUSIONS

A series of 47 consecutive cases of proved carcinoma of the thyroid gland have been reviewed, covering a seven and one-half year period.

Twelve hundred fifty-three operations were done on the thyroid during this interval, with an incidence of malignancy of 3.7 per cent.

Carcinoma occurred in 9.4 per cent of patients with non-toxic goiter with solitary nodules and in 5.3 per cent of patients with non-toxic multinodular goiter.

Carcinoma was found in 1 case of diffuse toxic goiter and in 1 case associated with chronic thyroiditis.

A marked preponderance of malignancy occurred in females—42 females to 5 males.

A preoperative diagnosis of suspected malignancy was made in 34 per cent of the cases. Histologic grouping of the tumors is given with their relative incidence and age range.

Papillary adenocarcinoma comprised over one-half of the histologic group.

The literature has been reviewed concerning the problems involved in the treatment of malignancies of the thyroid.

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CARCINOMA OF THE RECTUM

FACTORS RESPONSIBLE FOR RECURRENT OR RESIDUAL DISEASE*

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Because of incomplete surgical removal at the initial operation, residual cancer of the rectum continues to be a challenge to surgeons. To illustrate some phases of this problem a few tables will be presented that will demonstrate the current incidence of lymphogenous and venous metastasis. Data on survival and recurrence will be summarized in table form. The basic investigative research on the lymphatic drainage of the normal rectum as clarified by Villemain and Oliviera merits greater recognition. Their work offers a means of more accurately classifying rectal carcinoma by relating the location of the lesion to zones of lymphatic spread. An extension of the usual anterior and abdominoperineal surgical technics is presented for consideration. A partial solution to the problem of residual rectal malignancy should be attained if one advocates a more extensive initial surgical attack upon the cancer and its zones of spread.

LYMPHOGENOUS AND VENOUS METASTASIS

Perhaps the most striking evidence of the lethal nature of rectal carcinoma is the incidence of lymphogenous metastasis as revealed in table I and the frequency of venous metastasis as summarized in table II.

From this brief condensed information it is evident that, at the time of operation, over 50 per cent of patients with rectal carcinoma have lymph node metastases and more than 25 per cent of patients have venous metastases.

SURVIVAL AND RECURRENCE

Tables III to VI inclusive are informative for they clearly indicate that in patients whose rectal malignancy is located cephalad to the peritoneal reflection the five year survival rate exceeds 60 per cent and the recurrence rate is less than 10 per cent. For patients whose cancer is located below the peritoneal reflection the five year survival rate is less than 50 per cent and the recurrence rate is approximately 25 per cent.

LYMPHATIC DRAINAGE

The deficiencies in the lymphatic studies as summarized by Poirier, Cuneo, and Delamere¹⁹ and by others have been apparent for some time. The lymphatic drainage of the normal rectum as investigated by Villemain,²⁴ and confirmed by Oliviera,¹⁷ clearly indicate that the rectum should be divided into an upper intraperitoneal and a lower extraperitoneal portion. Anatomically and structurally

* From the Proctology Clinic of Washington, D. C.

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TABLE I
Lymph node metastases

Year	Author	Percentage of cases with involved nodes
1922	McVay ¹⁶	47
1933	Wood & Wilkie ²⁶	51
1934	Westhues ²⁵	59
1935	Gabriel, Dukes & Bussey ⁹	62
1938	Gilchrist & David ¹¹	68
1940	Coller, Kay & MacIntyre ⁴	64
1943	Seefeld & Barga ²¹	47
1951	Dunning, Jones & Hazard ⁸	57
1952	Grinnell & Hiatt ¹⁴	56

TABLE II
Venous metastases

Year	Author	Percentage of cases with involved veins
1938	Brown & Warren ³	61
1941	Coller, Kay & MacIntyre ⁴	15
1943	Seefeld & Barga ²¹	20
1944-45*	Dukes ⁷	17
1949†	Sunderland ²²	27.6
1950	Grinnell ¹³	36
1951	Dunning, Jones & Hazard ⁸	18.6

* Colon & Rectum. † Gross only.

TABLE III
Survival rate above peritoneal reflection

Year	Author	Operation	Survival 5 Yr.—%
1948	Gilchrist & David ¹²	ABP, OR	65.4
1948	Dixon ⁶	AR	67.5
1948	Dixon ⁶	ABP	57.9

ABP—Abdominoperineal; OR—Obstructive Resection; AR—Anterior Resection.

TABLE IV
Survival rate below peritoneal reflection

Year	Author	Operation	Survival 5 Yr.—%
1948	Gilchrist & David ¹²	ABP	51.8
1948	Dixon ⁶	ABP	42.1
1950	Pfeiffer & Miller ¹⁸	ABP	37.2

ABP—Abdominoperineal.

the landmarks for identification of the two levels are the middle valve of Houston and the peritoneal reflection. These are within 1 centimeter of each other. The middle valve of Houston will be located on an average of 10 centimeters from the external anal margin. The range of variation is between 9 and 12 centimeters.

The investigations of these authors may be summarized as follows:

The Upper Intraperitoneal Rectum. When Prussian blue dye (o) is injected into the mucosa of this segment it is collected exclusively by the lymphatic channels and nodes of the superior hemorrhoidal-inferior mesenteric vascular lymphatic pedicle. The dye is deposited in the nodes along the aortic-vena cava chain that ascends to disappear under the duodenum and pancreas. No dye is found to extend in a retrograde fashion caudal to the middle valve of Houston,

TABLE V
Recurrence rate cephalad to peritoneal reflection

Year	Author	Operation	Recurrence Rate—%
1949	David & Gilchrist ⁵	ABP	3.6
1940*	Garlock & Ginzburg ¹⁰	AR	4.9
1952†	Judd & Bellegie ¹⁵	AR	10.8

ABP—Abdominoperineal; OR—Obstructive Resection; AR—Anterior Resection.

*—Lesions 15 to 20 cm. †—Lesions 16 to 20 cm.

TABLE VI
Recurrence rate caudal to peritoneal reflection

Year	Author	Operation	Recurrence Rate—%
1949	David & Gilchrist ⁵	ABP	23.2
1950*	Garlock & Ginzburg ¹⁰	AR	30.
1952†	Judd & Bellegie ¹⁵	AR	34.3

ABP—Abdominoperineal; OR—Obstructive Resection; AR—Anterior Resection.

*—Lesions 7.5 to 10 cm. †—Lesions 10 cm. or less.

and no dye appears in the channels and nodes of the ileopelvic vascular lymphatic zone. The clinical inference to be drawn here is that lesions arising in the upper intraperitoneal rectum will, by preference, metastasize along the superior hemorrhoidal-inferior mesenteric-aortic-vena cava vascular lymphatic zone or pedicle. Figure 1 will illustrate these remarks.

The Lower Extraperitoneal Rectum. When cadmium yellow (X) is injected into the mucosa of this segment it is collected by and deposited in the cephalad abdominal channels and nodes and also by way of the middle hemorrhoidal-hypogastric-common iliac route. This is an ileopelvic zone. This pelvic pedicle also has collateral channels and nodes along the middle and lateral sacral zone, the upper vagina, broad ligament, uterus, bladder, seminal vesicles and prostate. Figure 2 will illustrate these remarks.

If the mucosa of the upper rectum has previously been injected with Prussian blue, the channels and nodes of the cephalad abdominal zone are stained green from the mixture of blue and yellow dye. Figure 2 again illustrates this for the combined dye zone is marked by o and X symbols. The clinical application to be made here is that lesions arising in the lower extraperitoneal rectum will metastasize to both the abdominal and to the pelvic zone.

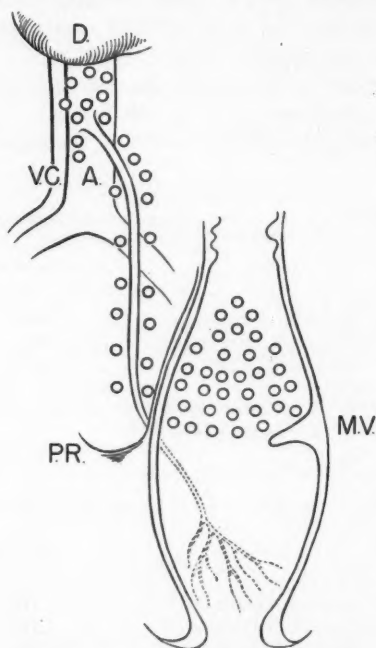


FIG. 1. Prussian blue dye (symbol o) injected into the rectal mucosa cephalad to the middle valve of Houston M.V. and the peritoneal reflection P.R. is collected exclusively in the cephalad superior hemorrhoidal-inferior mesenteric-aortic vena cava abdominal zone. D., aorta, V.C., vena cava. (Modified from Villemain and Olivier)

In summary, this basic information on the lymphatic drainage of the normal rectum clearly indicates that we have a well defined anatomical basis for the classification of rectal carcinoma into two groups:

1. Carcinoma of the upper intraperitoneal rectum should include those lesions located cephalad to both the middle valve of Houston and the peritoneal reflection. The caudal edge of these lesions should be 10 centimeters or more cephalad to the external anal margin.
2. Carcinoma of the lower extraperitoneal rectum should include those lesions located between the anus and the middle valve of Houston which is located at the same level as the peritoneal reflection.

THE LOCATION OF THE CARCINOMA

In our haste to classify rectal carcinoma by adopting various artificial levels, locations and zones we have almost completely ignored the two main divisions of the rectum as has been demonstrated by the foregoing investigations on lymphatic drainage. Many worthwhile operations have been brought into disrepute

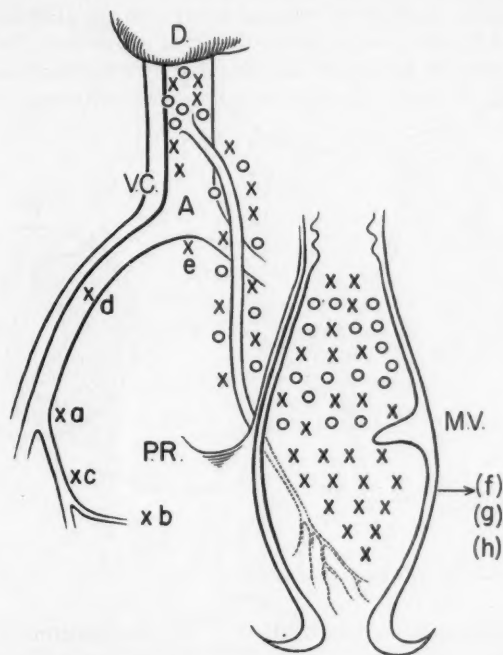


FIG. 2. Cadmium yellow (symbol X) injected into the rectal mucosa caudal to the middle valve of Houston M.V. and the peritoneal reflection P.R. is collected in the cephalad abdominal zone and into other pelvic zones such as the iliopelvic nodes Xa, the middle hemorhoidal nodes Xb, the hypogastric nodes Xc, the common iliac nodes Xd, the promontory and bifurcation nodes Xe, the middle and lateral sacral nodes Xf, the uterine broad ligament and vaginal collaterals Xg, and the seminal vesicle, bladder and prostate collaterals Xh. D., duodenum, A., aorta, V.C., vena cava. (Modified from Villemin-Oliviera)

because the surgeon classified his lesions according to the operation to which he was addicted instead of classifying them in relation to lymphatic drainage.

We wish to briefly summarize several years' work in which over 300 rectums and specimens have been measured. Measurements taken during operation have been correlated with the digital and proctoscopic examination. Some of our previous reports^{1, 2} will be clarified and in time we hope to present an accurate statistical analysis of our work. For the present, we have accumulated enough data to state that the average distance from the external anal margin to the

middle valve of Houston and to the peritoneal reflection is 10 centimeters. Figure 3A is informative. Prior to operation the distance from the external anal margin to the lower edge of the lesion is digitally and proctoscopically measured with the patient in the lateral Sims position. The degree of downward intussusception and the amount of fixation is estimated. These same estimates and measurements are again made with the patient in the inverted Hanes position. Figure 3B indicates whether the lesion is located on the anterior, posterior, or lateral aspects of the bowel wall and the degree of occlusion to the bowel lumen. The size of the lesion is estimated and other descriptive information is recorded. During operation we mark the level at which the peritoneum reflects off the

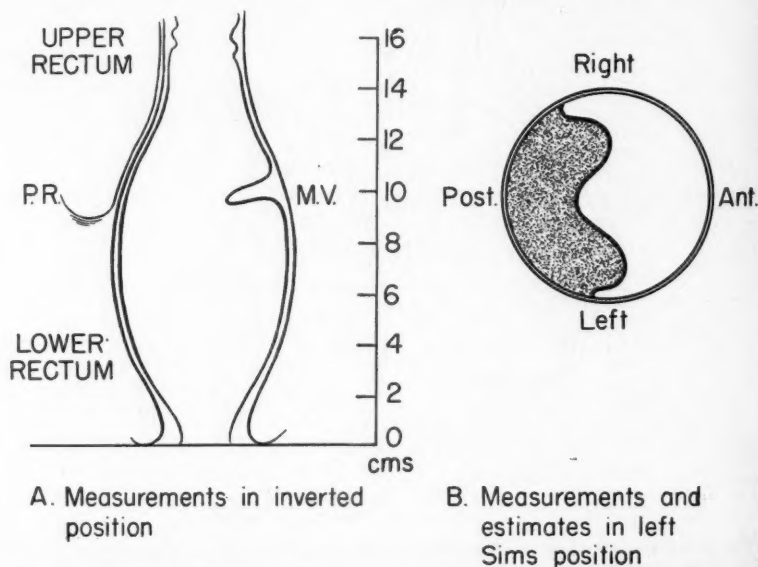


FIG. 3. Diagram illustrating (A) the average distance from the external anal margin to the middle valve of Houston M.V. and the peritoneal reflection P.R. and (B) the circumferential location of the lesion and the degree of encroachment of the bowel lumen.

anterior muscular coat of the rectum. If the lower edge of the malignancy is cephalad to the peritoneal reflection as determined by correlating the preoperative measurements with the localization at operation, we believe that we have correctly designated the malignancy as carcinoma of the upper rectum. Malignancies of the lower rectum are much less mobile and they rarely present any difficulty in localization.

Malignancies of which major portions extend above or below the peritoneal reflection should be considered as individual problems. Space will not permit a discussion of the small number thus classified. However, it has been our experience that the majority of rectal carcinomas can be classified into the two main divisions as heretofore outlined.

Having classified lesions more accurately according to their sites of origin, as related to their lymphatic drainage, the next step should be to determine the operative procedure designed for adequate removal of the zone of lymphatic spread. Proper provision should be made for those lesions in which the areas of growth and zones of metastasis actually overlap the anatomical boundaries outlined.

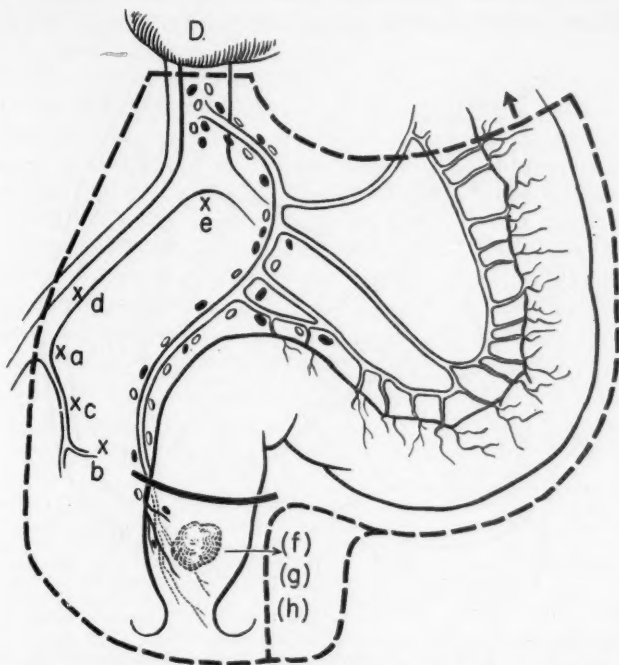


FIG. 4. Carcinoma of the upper rectum. This illustrates removal of the cephalad superior hemorrhoidal-inferior mesenteric-aortic vena cava zone of lymphatic spread. Division of the colon as indicated by the arrow may be extended in a cephalad direction. The peritoneal reflection is indicated by the heavy line across the rectum caudal to the lesion.

SURGERY OF CARCINOMA OF THE UPPER RECTUM

We believe that most lesions of the upper intraperitoneal rectum can be adequately resected by what may be considered an extended anterior resection.¹ An extended Hartman resection is advocated for those patients whose conditions do not warrant removal of the extraperitoneal rectal stump. Our present conception of an adequate anterior resection consists of a wide pelvic dissection extended to include visualization of the cephalad surface of the levators. The inferior mesenteric artery is ligated at its aortic origin and the fascia, intermesenteric plexus and aortic-vena cava lymphatics are removed in continuity from the lower border of the duodenum to and including the nodes at the aortic-vena cava bifurcation and at the sacral promontory. The inferior mesenteric vein is ligated as it disappears under the duodenum. Upon completion of this

cephalad zone of lymphatic vascular dissection it is frequently necessary to mobilize the splenic flexure or even the transverse colon so that the end of the bowel may be brought down to the pelvis. The rectum should be divided at least 5 or 6 centimeters distal to the growth, and any compromise with this should be classified as an inadequate operation. Anastomosis of the colon to the rectal stump completes the procedure in most instances. Figure 4 illustrates some of the previous discussion.

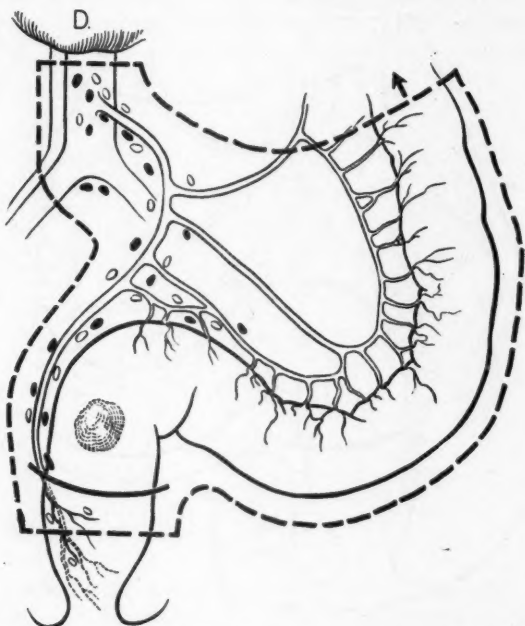


FIG. 5. Carcinoma of the lower rectum. This illustrates removal of the cephalad zone of lymphatic metastasis and the ileopelvic zones of metastasis. The symbols Xa to Xh refer to clearance of lymphatics diagrammed in figure 2 and mentioned in the text of this article.

SURGERY OF CARCINOMA OF THE LOWER RECTUM

Lesions of the lower extraperitoneal rectum should be removed by what we consider an extended abdominoperineal resection^{14, 2} which may be classified as a partial exenteration. We have previously reported our experience in ligating the inferior mesenteric vessels at a higher level than has been recommended by Miles. This same extensive cephalad zone of removal is performed as recommended for anterior resection. In selected cases a panhysterectomy is done which includes removal of the adnexa from the lateral pelvic wall. Unilateral or bilateral ureteral resection with concomitant ureterointestinal anastomoses or or ureterovesical implantation is done when these structures are involved. Seminal vesiculectomy for ventrally placed lesions is advocated and in some instances partial cystectomy will be necessary. Additional ileopelvic and obturator

node dissection is sometimes facilitated by a two-team abdominoperineal synchronous procedure. During the perineal phase wide resection of the levators and vaginectomy is mandatory for the adequate removal of local infiltration of low lying lesions. Figure 5 illustrates some the the previous discussion.

SUMMARY

If one analyses the existing literature on this subject it is evident that the failure of surgeons to properly classify rectal carcinoma has been compounded for some time. The adoption of artificial levels and zones that relate the malignancy to the operative procedure instead of relating it to zones of lymphatic spread should be corrected. The correlation between the location of the lesion with respect to the middle valve of Houston and the peritoneal reflection merits greater consideration. Operative procedures indicated for extended resections and extirpation of both the lesion and its lymphatic-vascular zones of dissemination are briefly outlined. There is increasing interest in the extended types of operation.^{14, 20, 23} Partial solution to the problem of recurrent or residual carcinoma should be forthcoming if the lesion is more accurately located in relation to its lymphatic drainage and if the operation is designed and performed to remove the zones of lymphatic metastases.

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PREMALIGNANT LESIONS OF THE GASTROINTESTINAL TRACT

II. THE SIGNIFICANCE AND MANAGEMENT OF POLYPS OF THE COLON*

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INTRODUCTION

It has been estimated¹⁰ that reported and unreported deaths from carcinoma of the colon and rectum number at least 30,000 a year in the United States. No standard figures are available regarding the number of persons who develop the disease and are treated successfully. While some authors report 42 to 68 per cent relative five year survival rates among those patients with tumors which are resected^{6, 8, 14} it is generally agreed that the absolute survival rate for the country as a whole is much lower, probably close to 15 per cent. These figures indicate the need for new methods and a change in view-point if the hitherto discouraging results in the management of carcinoma of the colon are to be improved.

In a previous paper² it was suggested that the problem of carcinoma of the stomach might be attacked by a thorough search for the premalignant lesion of chronic hypertrophic gastritis, followed by prophylactic gastric resection. Similar identification of lesions known to be premalignant in the colon, and adequate removal of them, might be expected to considerably reduce the incidence of cancer in this organ, and thus reduce the number of annual deaths from this disease to a significant degree.

It has been shown conclusively that polyps occur with greater frequency in people over 50 years of age. Atwater and Barger¹ observed no polyps before the fourth decade of life and reported that the mean age of the patients in whom polyps were found was 64 years. By counting very small polyps they found 69 per cent of the autopsy specimens in the older age group studied by them to show polyps. On the other hand, Lawrence⁹ found 2.37 per cent in 7,000 autopsies; Swinton¹⁸ 7 per cent in 1,843 consecutive autopsies, and Helwig⁷ 9.5 per cent in 1,460 autopsies. It is difficult to establish a satisfactory percentage for the true incidence of polyps of the colon but there is no doubt that the frequency is much higher in the selected age group susceptible to cancer. Furthermore, it is a widespread clinical impression that these lesions are *increasing* in frequency. It would appear as if the development of polyps in the colon were part of the natural aging process akin to proliferative changes in the prostate and breast which are so common in later life.

Furthermore, polyps in the colon show a definite potentiality for malignant degeneration. In Lawrence's series of 7,000 autopsies, when the incidence of

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polyps was 2.37 per cent, the incidence of malignancy in the polyps was found to be 6.5 per cent. Colvert and Brown⁵ reported 5.9 per cent malignancy in 235 cases of rectal polyps although they cite widely divergent figures from the literature. It is probable that the development of carcinoma in polyps elsewhere in the colon is much more frequent. Rectal polyps may be expected to give symptoms earlier and be discovered more easily than those located elsewhere in the colon. And, as will be shown, the length of time during which a polyp remains silent bears a relationship to the development of cancer. Furthermore, it is well

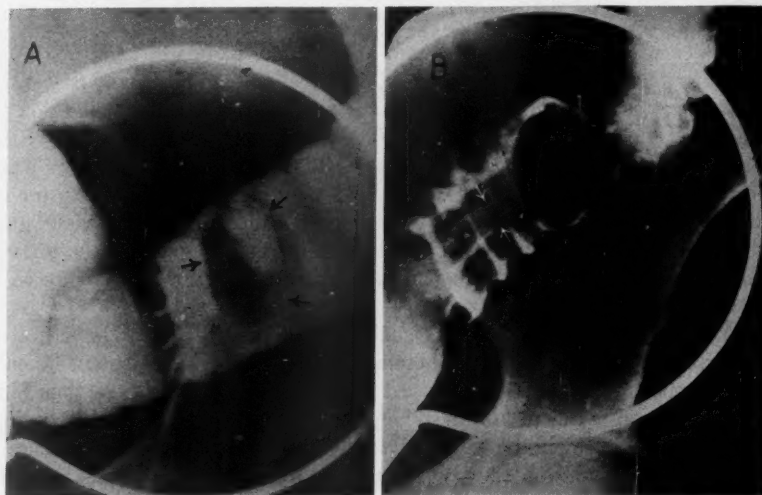


FIG. 1, Case 1. Large solitary polyp in the sigmoid colon in a patient with recent bleeding from the bowel. The left half (a) of the figure shows the appearance with compression during filling of the bowel with barium. Note the solitary filling defect caused by the polyp and the drawing in of the bowel wall due to traction by the pedicle. The figure on the right (b) shows the appearance after evacuation and injection of a small amount of air. Compression now shows the characteristic scalloped border of the polyp and the long pedicle seen through the air column.

It is often very difficult to palpate a polyp, even as large as this, through the intact bowel wall at the time of the exploratory laparotomy, so that the precise identification and location of the polyp during the roentgenologic study is of considerable importance.

known that members of families showing multiple polyposis of the colon have an extremely high incidence of colonic carcinoma. In view of the above facts, it is probable that many, if not all, carcinomas of the colon may arise from pre-existing polyps. It would appear, therefore, that a large part of the management and control of carcinoma of the colon, depends primarily upon the recognition and eradication of the premalignant polyp which may be its ancestor.

The various manifestations of the natural history of polyps in the colon and the problems encountered in the treatment of them may be illustrated by the following examples:

CASE REPORTS

Case 1. B. M., a white woman, aged 50, had recent painless rectal bleeding. Digital examination of the rectum and sigmoidoscopy gave negative findings. A barium enema re-

vealed a large solitary polyp in the middle sigmoid which was subsequently removed (fig. 1).

Comment: Polyps of the colon are common in middle-aged and elderly people. This is the typical appearance of what may be a premalignant polyp in the colon. This patient might well have developed a carcinoma at this site if the polyp had not been removed.

Case 2. E. R., a middle-aged white woman had painless rectal bleeding and negative physical and sigmoidoscopic examinations. The double contrast study following a barium enema



FIG. 2. Case 2. Contrast enema with air showing the distal transverse colon and the descending colon in a patient with painless bleeding from the bowel. Note the two polyps in the middle of the descending colon which appear to project from short, wide pedicles. The inferior polyp is associated with slight retraction of the margin of the bowel at the insertion of the pedicle. By demonstrating the pedicle in the air study one can exclude the possibility of shadows being due to fecal material or bubbles of air.

clearly demonstrated two polyps in the descending colon, which were subsequently removed (fig. 2).

Comment: Polyps of the colon are frequently multiple. If a single polyp is found, one should assume there are more polyps until thorough study proves otherwise. Removal of one polyp will not protect the patient from the development of carcinoma derived from another polyp which has been overlooked.

Case 3. L. S., a white woman, aged 56, had painless rectal bleeding for several months. Repeated examinations elsewhere had not shown any disease. Physical and sigmoidoscopic examinations were noncontributory. A barium enema showed a large polyp in the sigmoid and a smaller polyp below the splenic flexure (figs. 3 a and b). The latter was overlooked in the interpretation of the roentgenograms. The polyp in the sigmoid was removed and

the patient was well for the following five years. In the course of a follow-up survey of all patients with roentgenologic diagnosis of colonic polyps over a 10 year period, this patient

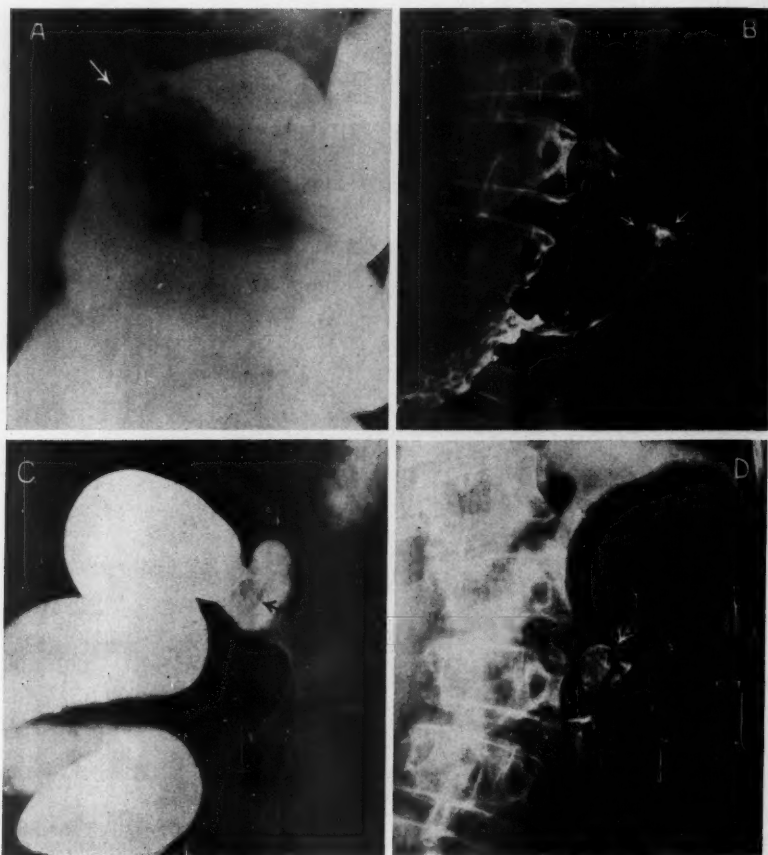


FIG. 3, Case 3. A 56 year old white woman was first seen in 1944 because of painless bleeding per rectum. Repeated examinations elsewhere had not shown any disease. The barium enema study showed a large polyp in the lower sigmoid (a) and a smaller polyp just below the splenic flexure (b). This second polyp was overlooked in the interpretation of the roentgenograms. The polyp in the sigmoid was removed and the patient was well for the following five years.

A second barium enema examination five years later showed a small polyp in the mid-portion of the sigmoid several centimeters above the site of the previous operation, (c) and the polyp at the splenic flexure which had about doubled its size (d). Both of these polyps were removed, and at the same time the patient was found to have a diseased gallbladder which the surgeon believed was on the point of perforation. The gallbladder also was removed.

This sequence of events illustrates the role of prophylactic medicine in dealing with the problem of carcinoma of the colon.

was asked to return for another barium enema. She was reluctant to do so because she had no symptoms. Re-examination by barium enema, however, revealed a new polyp near the site of the previous resection and showed, in addition, that the polyp at the splenic flexure

had increased in size (figs. 3 c and d). Both of these lesions were subsequently resected and at the same time the surgeon removed the gallbladder which was badly diseased.

Comment: This story illustrates that polyps, even though benign, may slowly increase in size over a period of years. Of even more significance is the fact that polyps may recur either at the site of resection or elsewhere in the colon. *This means that periodic and complete examination of the large intestine should be done at least annually in all patients from whom polyps have been removed.*

Case 4. A. K., a middle-aged white man had had an abdomino-perineal resection for carcinoma of the rectum. He remained well for four years and returned complaining of slight

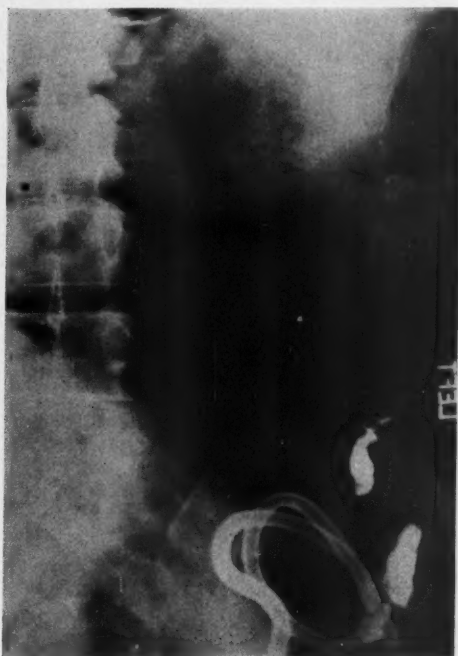


FIG. 4. Case 4. Double contrast enema was done through a colostomy. The transverse and descending colon is outlined by means of the barium and air. Note the solitary polyp in the middle of the descending colon several inches above the colostomy.

This patient had had carcinoma of the sigmoid removed four years previously by abdominoperineal resection. He had been perfectly well until recently when he noted a small amount of serosanguineous discharge from the colostomy opening.

This indicates that polyps are not only multiple but are successive in their occurrence.

serosanguinous discharge from the colostomy. A barium enema followed by air injection of the colon disclosed a small polyp in the descending colon (fig. 4), which was subsequently resected.

Comment: Because of the etiological relationship between polyps and carcinoma and the fact that polyps are frequently multiple, the discovery of a carcinoma in the colon should make it mandatory that the remainder of the bowel be carefully searched for associated polyps. Furthermore, patients from whom a carcinoma of the colon has been removed, should be studied by roentgenologic methods at least annually, not only to detect recurrence of the original carcinoma but also to discover newly developed polyps.

Case 5. E. B., a middle-aged white man was complaining of weakness, weight loss and

anemia. A barium enema disclosed a large polypoid carcinoma in the ascending colon and multiple polyps in the descending colon and sigmoid (fig. 5). Because of the patient's poor physical condition, only the carcinoma was removed.

Comment: This illustrates the common association of polyps with carcinoma, which must be kept in mind by the roentgenologist and surgeon. When polyps are widely scattered in the colon, the decision as to proper therapeutic approach may be difficult.

Case 6. S. W., a middle-aged white man complained of rectal bleeding. Double contrast barium-air study showed many polyps scattered along the descending colon and sigmoid (fig. 6 a). A resection of the sigmoid and descending colon was done in the hope of including



FIG. 5, Case 5. Double contrast barium enema in a middle aged patient complaining of anemia, weakness and weight loss. Note the large, irregular polypoid mass arising from the medial wall of the ascending colon. In addition, there is a large polyp seen in the middle of the descending colon and the original study suggested the presence of other polyps which are not clearly demonstrated here. The lesion in the ascending colon was removed and proved to be a polypoid carcinoma. Because of the patient's poor condition no further surgery has been done.

This illustrates the simultaneous occurrence of carcinoma and multiple polyps. This combination has been estimated to occur in about 30 per cent of patients with carcinoma.

all of the lesions. The specimen showed a carcinoma in the lower sigmoid and many polyps of varying size (fig. 6 b). The cut edge of the superior part of the specimen passed directly through a small polyp which the surgeon had not recognized at the time of operation. A postoperative barium enema and air study showed residual polyps scattered along the colon as far back as the hepatic flexure (fig. 6 c).

Comment: This is an extreme example of the association of carcinoma and polyps. In this patient any treatment short of total colectomy would be inadequate to protect from the probability of developing another carcinoma at some future time.

Case 7. W. J., a 50 year old white man, was first seen in 1947 with bloody diarrhea. The barium enema demonstrated a large polyp in the sigmoid (fig. 7 a), which was overlooked

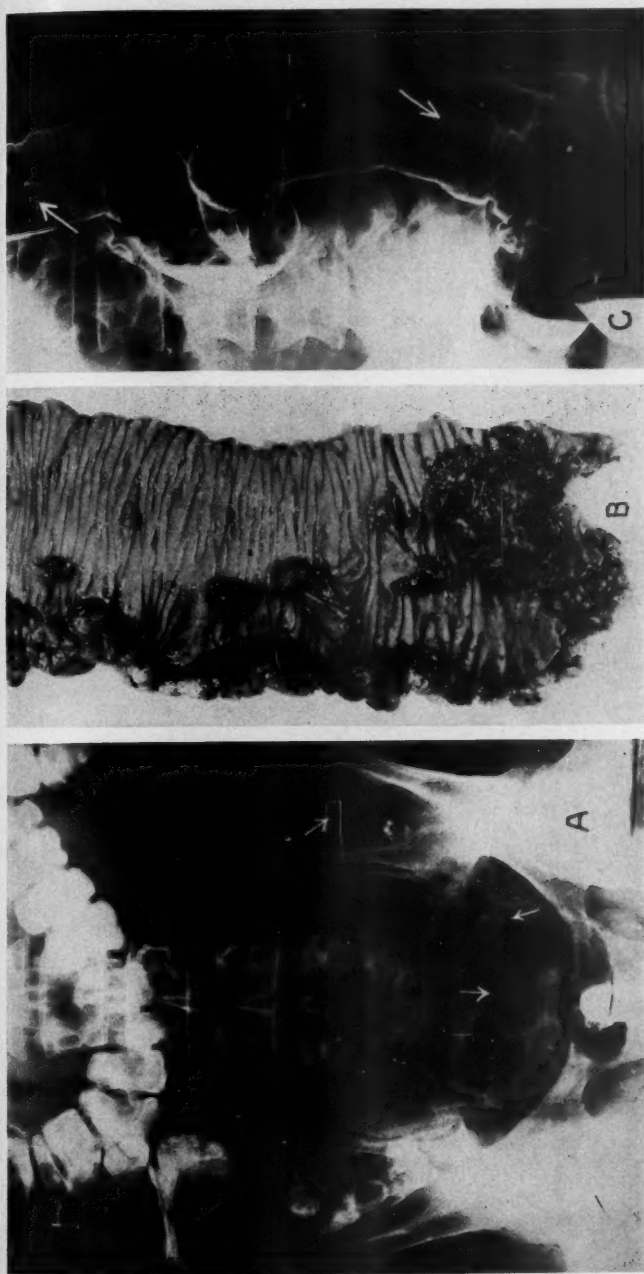


FIG. 6. Case 6. Air study of the colon following barium enema in a middle aged white man with rectal bleeding. Note the numerous polyps in the sigmoid and descending colon some of which are indicated by the arrows (a). A generous portion of the sigmoid was resected in an attempt to include all of the polyps. The resected specimen showed a carcinoma at the lower edge of the removed bowel and many satellite polyps around the carcinoma and extending upward along the bowel (b). As a matter of fact, the resection passed directly through one of these polyps which was not identified at the time of operation.

The follow-up barium enema made several months later at a time when the patient had no symptoms demonstrated at least three residual polyps in the descending colon and the proximal colon shown best in the double contrast roentgenogram. These are indicated by arrows (c). This illustrates the fact that when multiple polyps are present it is often impossible to determine the extent of the disease, and one may expect residual polyps unless a complete colectomy is done.

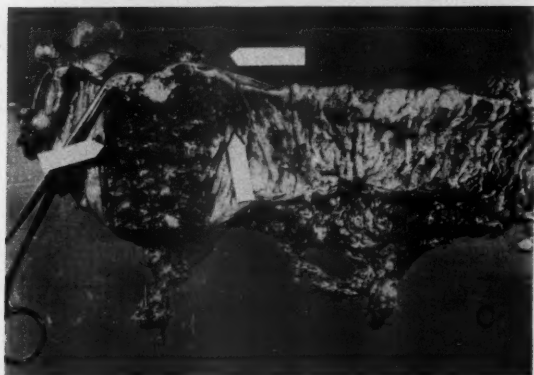


Fig. 7. Case 7. A 50 year old white man was seen first in 1947 complaining of diarrhea and bloody bowel movements. The first examination was interpreted as showing nothing abnormal. Actually the roentgenograms demonstrated a large polyp in the sigmoid which was overlooked. This is shown in the air study (a). In the next two years the patient had recurrent bleeding and was examined on several occasions, always with a negative interpretation. The last examination was exactly two years later in 1949 at which time an irregular infiltrating carcinoma of the sigmoid was found (b). This occupied the area where the original polyp had been present. The specimen removed at operation confirmed the diagnosis of an infiltrating carcinoma and in addition showed numerous satellite polyps at the periphery of the lesion (c).

This is an example of the natural history of many of these polyps of the colon. When they are as large as this one at the time they are first discovered one can anticipate malignant degeneration within one or two years.

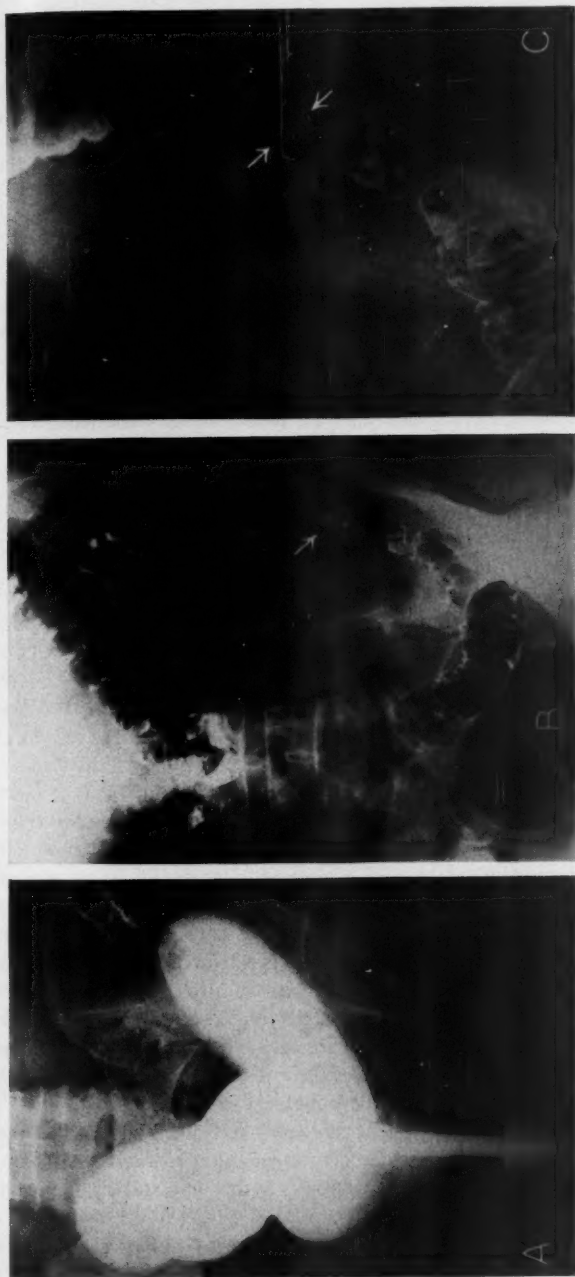


FIG. 8. Case 8. A 55 year old white woman was first seen in 1947 with symptoms of obstruction of the lower bowel. A barium enema showed a lesion in the upper portion of the sigmoid which was producing complete obstruction to the retrograde enema. There was a polypoid element to the lesion (a). The next examination was done one year later. The patient had no symptoms. The area of the anastomosis is shown by the lower arrow. Above this site there is a filling defect which is due to another polyp (b). Because of the patient's medical condition reoperation was not done.

The last examination in 1949 showed a change in the appearance of the recurrent polyp. At that time there was a fixed deformity of the lateral wall of the descending colon and a slight reduction in the caliber of the bowel at the site of the polyp (c). This suggests that the polyp had begun to infiltrate the wall of the colon and had become malignant.

This sequence of events indicates the occurrence of successive polyps with successive carcinoma due to malignant degeneration.

by the examiner. The symptoms continued, and in 1949 a barium study revealed an irregular infiltrating carcinoma at the site previously occupied by the polyp (fig. 7 b). The resected specimen showed carcinoma with numerous satellite polyps (fig. 7 c).

Comment: This is a thumb-nail sketch of the natural history of many malignant neoplasms of the large intestine and demonstrates the price which is paid when polyps in the colon are neglected or overlooked.

Case 8. M. G., a 55 year old white woman was examined in 1947 because of intestinal obstruction. A barium enema revealed a polypoid mass obstructing the sigmoid (fig. 8 a). A colostomy was done in the mid-transverse colon, and the carcinoma of the sigmoid was resected with primary end to end anastomosis of the bowel. A follow-up barium enema 10 months later showed irregularity of the bowel at the site of anastomosis and at the site of the previous colostomy, but no evidence of carcinoma.

The next study was made in 1948. The patient had no symptoms. A new polyp was discovered just above the former anastomosis in the sigmoid (fig. 8 b), but because of the patient's poor physical condition no operation was done.

The last barium enema was done in 1949. The patient still had no complaints. The recurrent polyp presented a changed appearance. It was flatter and there appeared to be a fixed deformity of the bowel wall at its base (fig. 8 c). These findings suggested that the polyp had become malignant and invasive. No operation has been done.

Comment: This history illustrates the following facts: Carcinoma of the colon may develop from a polyp; where there is one polyp or carcinoma there may be others either concomitantly or successively; and where there is one carcinoma of the colon there may be others either coincidently or successively.¹⁵

DISCUSSION

Radiologic considerations. In discussing the diagnosis of polyps of the large intestine it should be unnecessary to reiterate the importance of the digital examination of the rectum and the importance of sigmoidoscopy. These procedures should be a part of every physical examination and, if properly done, should reveal 60 per cent of all neoplastic lesions of the colon.^{5, 6} While all physicians give lip service to this principle, these examinations are often postponed, because of the inconvenience and discomfort involved, until it is too late.

For the examination of the colon above the rectum, roentgenologic procedures are of paramount importance. Numerous recent papers^{3, 11, 17, 19} have described the technics and evaluated the results of this method of study. Of these technics the use of barium and air as double contrast media are of fundamental importance. Furthermore, it should be emphasized, that the barium enema examination is one of the most difficult of roentgenologic procedures, if properly done, and requires meticulous care and considerable expenditure of time and effort. Even under the best circumstances it will often be necessary to repeat the entire study once or several times to evaluate adequately equivocal findings. Experience has shown that if one makes a conventional barium enema study under fluoroscopic guidance, it may not be possible to follow this immediately with a good air study. For this reason it is advisable to inform the patient and his referring physician that two separate and complementary examinations may be necessary on different days, when the patient's symptoms and signs suggest polyps of the colon.

Surgical Considerations. The recent literature contains numerous carefully presented papers^{4, 12, 13, 15, 16} dealing with the surgical care and end results in

polyps of the colon. Difficult as it often is to demonstrate large bowel polyps by roentgenologic means, it is even more difficult to identify them by palpation during an exploratory laparotomy. This is due, in part, to the fatty attachments of the colon—the omentum, the appendices epiploicae, and the irregular distribution of mesenteric fat along the sides of the bowel. Feces, too, may make palpation confusing. Therefore, it is infrequent that polyps of the colon are found at exploratory laparotomy unless; (1) they have given rise to some other lesion such as intussusception, or, (2) they have been previously localized.

While most surgeons will agree that roentgenologic study is the best approach to the diagnosis of polyps, the limitations of this method of examination should be recognized. Frequently specimens of resected bowel show additional polyps not previously demonstrated by barium enema and, on the other hand, the identification of one or more polyps on a single examination without confirmation by a second study may lead to a *false positive* diagnosis.

If a polyp is located roentgenographically, it may sometimes be approached through the proctoscope or sigmoidoscope and tissue for biopsy obtained. In general, this should not remove the entire polyp unless one has some method of marking the site from which it came. It may be impossible to recognize the place later, should the biopsy reveal malignancy. One method of marking consists in the injection through a long needle of a small quantity of india ink into the mucosa. This makes a sort of tattoo which apparently remains indefinitely.

If it is determined that the lesion is benign, its removal through the proctoscope or sigmoidoscope may be completed, usually by means of the high frequency current. The disadvantages of the proctoscopic route of removal are the danger of perforation and hemorrhage. The effort to avoid these hazards may, at times, result in a *skimpy* or even incomplete removal of the lesion.

Many of the polyps revealed by roentgenologic studies are above the range of the 10 inch sigmoidoscope (usually a little over half way between the symphysis pubis and the umbilicus). These must be approached transabdominally, the incision being varied according to the location of the polyp. A liberal incision is needed for the exploration even though the polyp is small. The portion of the bowel affected is mobilized by cutting the necessary lateral attachments. The antimesenteric border is freed of adherent fat tabs and the region carefully searched for masses that slip through the fingers on palpation. If the polyp is felt, it is distinguished from feces by the presence of an attachment to the bowel. Colotomy is then done opposite, but not through the pedicle, and the lesion is excised with all of the pedicle, and a zone of normal mucosa surrounding it, leaving the muscularis intact. The mucosal wound is closed with running sutures from inside the bowel and then the colotomy wound is closed transversely in layers with the usual inversion of the mucosa.

As soon as such a specimen is delivered, it should be sent to the pathologist for frozen section. If there is invasion of the stalk, or other discernible evidence of malignancy, resection of the bowel should be done; but if no such evidence is forthcoming no further tissue need be removed and the colotomy closure may be completed.

It sometimes appears that, following the procedure as outlined above, the pathologist finds evidence of carcinoma in the paraffin sections. If this shows invasion of the pedicle, a second operation with resection of bowel and mesentery would seem indicated. However, if only a carcinoma *in situ* is found at the tip of a polyp with a fairly long stalk, some surgeons believe that it is safe not to resect the segment of bowel but merely to keep the area under observation by roentgenologic examination at three to six month intervals. While we know of a good many instances in which this policy has been followed successfully, it obviously depends to a considerable extent upon the judgement of the surgical pathologist. Probably, more experience must be accumulated before final conclusions can be drawn.

When carcinoma *in situ* is found after removal of a polyp in the area visualized by the proctoscope or sigmoidoscope one is often troubled because it is difficult to know how thorough the removal actually was. If the lesion is in the distal 6 or 8 cm. of the rectum it is often possible to dilate the sphincter thoroughly and draw the lesion down far enough to excise it under direct vision. However, if the polyp is *higher up*, it is more satisfactory to remove it transabdominally, if it is intraperitoneal, or through an incision behind the anus (often with removal of the coccyx), if it is in the upper rectal segment but below the probable level of the peritoneal reflection. Through such an incision, the rectum can be mobilized and a patch of rectal wall bearing the polyp can be removed.

At times, abdominal exploration and palpation of the bowel fail to locate a polyp previously demonstrated by roentgenologic examination. It then becomes necessary to open the bowel in the area where the polyp was identified by barium enema and look up and down the bowel with a previously sterilized sigmoidoscope. If the bowel can be made clean and the scope passed 6 to 10 inches in each direction, it should be possible either to find the polyp or to rule out its existence in the area studied.

Transillumination of the colon is another valuable adjuvant in finding polyps of the colon at the time of laparotomy. A sterile transilluminating device should be at hand in the operating room for this purpose.

SUMMARY

Present treatment of patients with *frank* carcinoma of the colon results in relatively few five year survivals. Many patients over 50 years of age develop polyps in the colon. These polyps often become cancer. For these reasons, the diagnosis and removal of colonic polyps which may still be nonmalignant, represents an important contribution to the reduction in incidence of carcinoma of the colon, and thus in its control.

Factors in the roentgenologic diagnosis and surgical treatment of colonic polyps have been reviewed. In many patients polyps occur successively. Therefore, periodic follow-up examinations of the colon by sigmoidoscopy and barium enema studies are mandatory in any person who has been treated once for carcinoma or polyps of the large intestine.

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EARLY AND DELAYED OPERATION FOR ACUTE CHOLECYSTITIS*

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Differences of opinion concerning the methods of treatment of acute cholecystitis still exist. Surgeons almost all agree that cholecystectomy is the treatment of choice, but some of them disagree about the timing of the operation.³ Cholecystostomy as a treatment of acute cholecystitis is now rarely considered except in those patients who are very poor operative risks. Prior to 20 years ago little was heard about early operation for acute cholecystitis. Interest in the early treatment of acute cholecystitis by cholecystectomy was definitely stimulated by reports made by Stone and Owings¹² in 1933 and by Heuer⁷ in 1934. In the last 15 to 20 years a rapidly increasing number of surgeons have expressed their preference for early operation and have presented proof in their statistics that operation within 48 hours of the onset of symptoms of acute cholecystitis has reduced both mortality and morbidity rates.^{5, 1}

We present a small series of patients who have been treated at the University of Kansas Medical Center in a 10 year period ending July 1, 1952. There have been hospital records of 205 patients with diagnoses of acute cholecystitis or acute and chronic cholecystitis. These patients are divided into four groups for convenience of analysis. Of this number 75 had clinically acute cholecystitis when admitted to the hospital. We have considered only those patients who had fever, leucocytosis of 10,000 or higher, and localized tenderness in the gallbladder region as having had clinically acute cholecystitis. In many instances there was a palpable gallbladder and nausea and vomiting.

The following tables I to V summarize the study made of the 205 patients.

These tables indicate that operations upon patients with acute cholecystitis or subsiding acute cholecystitis have no greater mortality rate than those operated upon after a long delay following the acute attack. The 2 patients with clinically acute cholecystitis who died were not operated upon. Autopsies showed that 1 of these had an acute perforation into the free peritoneal cavity and the other had an acute cholecystitis with cholangitis and multiple abscesses of the liver. We do not know the fate of the 20 patients who left the hospital without operation and did not return. In all of these 20 patients the acute attacks had subsided before the patients were discharged from the hospital. The records indicate that their clinical diagnoses were correct.

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There were 12 patients in Group II and 13 patients in Group III whose diagnoses were not proved by operation or autopsy. A review of the records

TABLE I

Number of patients with diagnoses of acute or acute and chronic cholecystitis

Group I	Clinically acute cholecystitis	75
Group II	Clinically acute cholecystitis (probably gallstone colic)	13
Group III	Clinically acute cholecystitis (doubtful)	25
Group IV	Pathologically acute or acute and chronic (clinically chronic)	92
Total number of patients		205

TABLE II

Patients having clinically acute cholecystitis

Group I

Total number	75
Total number operated upon	53
Operation during first hospitalization	42
Discharged and readmitted for delayed operation	11
Number discharged who failed to return	20
Postoperative deaths	0
Number of deaths (no operation) (autopsies)	2 (2.6 per cent)

TABLE III

Further data—53 patients of Group I who were operated upon for acute cholecystitis

Total number operated upon	53
Cholecystectomies	52
Cholecystostomies	1
Number jaundiced	11 (20.7 per cent of total)
Number common ducts explored	16 (30.1 per cent of total)
Stones found in common duct	11 (20.7 per cent of total)
Number pathologically proved acute	53
Common duct complications	0

TABLE IV

Timing of operations in Group I

Number of patients operated upon in first 48 hours	4
Number of patients operated upon 48 to 96 hours	4
Number of patients operated upon after 96 hours	34
Number of patients discharged and readmitted for operation	11
Total	53

suggests that the final clinical diagnoses should be considered doubtful in some of the patients in these two groups. There were three deaths without autopsies

in Group III. It is very doubtful if the deaths were due to gallbladder disease.

In Group IV, 92 were operated upon and diagnoses of acute or acute and chronic cholecystitis were made by the pathologists. Two of these patients died. There was one autopsy. The causes of death were cardiovascular disease in 1 and the other followed an operation for bleeding esophageal varices. The diagnosis of acute cholecystitis in the second case was made at autopsy.

TABLE V

Analysis of 130 (205 less 75) patients with diagnoses of acute or acute and chronic cholecystitis made by clinician or pathologist

Group II	
Number probably having gallstone colic (no fever or leucocytosis)	25
Cholecystectomies in this group	13
Proved by pathologist—acute or acute and chronic	13
No operation	12
Group III	
Number doubtful—diagnosed acute cholecystitis by clinician	13
Operated upon	0
Deaths (no autopsy)	3
Group IV	
Number clinically chronic but pathologically acute	92
Number operated upon (91 cholecystectomies)	92
Death (postcholecystectomy)	1
Death (operation for bleeding esophageal varices; autopsy—acute cholecystitis)	1
Common duct strictures	2

TABLE VI

Late complications of acute cholecystitis (not included in the series of 205)

Cholecystoduodenal fistula (no operations) (ages 55, 58)	2
Choledochoduodenal fistula (operation) (age 65)	1
Intestinal obstruction due to gallstone (operations) (2 deaths) (ages 53, 77, 77)	3
Cholecystocutaneous fistula (operation) (age 72)	1
	7

Two patients in the group of 92 with pathologic diagnoses of acute or acute and chronic cholecystitis developed strictures of the common duct following cholecystectomy. Both of these strictures were due to postoperative infections and not to injury at operation.

Another group of patients with complications of gallbladder disease not included in the series of 205 are listed in table VI. These patients were treated in the hospital during the same 10 year period as the other patients recorded. Two of this group with intestinal obstructions due to gallstones died following operations. One died of acute peritonitis and the other from the result of a 10 day

period of bowel obstruction and nephritis. These 7 patients are examples of remote complications of gallbladder disease.

DISCUSSION

Every surgeon of experience knows that many gallbladders which have been removed will show evidence of acute cholecystitis when the patients present no clinical evidence that the disease is acute. Patients in this group are not the ones who are in danger. While it is recognized that an occasional case of acute cholecystitis, with minimal clinical signs and symptoms, may have serious complications, certainly this is not the rule. Mentzer⁹, in 1932, noted that 3 of his patients with acute infections had no localized abdominal tenderness. One of these patients had a perforation of the gallbladder, 1 had an acute exacerbation of chronic empyema of the gallbladder with free pus in the peritoneal cavity, and the third had an acute empyema. Those patients who are in danger of gangrene, perforation and the formation of pericholecystic abscess are usually very readily distinguishable by their signs and symptoms. These are the patients who have stimulated discussion and disagreement concerning the choice of treatment.

It is safe to say that there always has been a difference of opinion concerning the treatment of acute cholecystitis. This difference of opinion has been discussed by many of the leading surgeons of the world. In many discussions it has not been made clear just what the authors meant by acute cholecystitis. Acute cholecystitis as diagnosed by the clinician and by the pathologist may be vastly different from the standpoint of mortality rate, and the two groups should definitely be separated. Ross, Boggs and Dunphy¹¹ have clearly shown that when acute cholecystitis develops, inflammation, fibrosis and scarring may continue for weeks, months or possibly years. Patients having late pathologic evidence of acute cholecystitis, without acute clinical symptoms, should not be placed in the same category as those having clinically acute cholecystitis when mortality rates are studied.

Definition of acute cholecystitis. Clinically acute cholecystitis produces pain, fever, leucocytosis and acute abdominal tenderness in the gallbladder area. Other signs and symptoms frequently present are a palpable mass, muscle spasm and nausea and vomiting. The acute cholecystitis or acute and chronic cholecystitis diagnosed by the pathologist may have very little clinical evidence of an acute infection when seen by the surgeon, or may give a history of acute infection—sometime in the past—which has subsided.

Definition of perforation of the gallbladder. Niemeier¹⁰, writing in 1934, realized the importance of differentiating between types of gallbladder perforations and classified them as follows:

1. Chronic perforations with the presence of a fistulous communication between the gallbladder and some other viscus.
2. Subacute perforations in which the gallbladder is surrounded by an abscess, walled off by adhesions from the general peritoneal cavity.
3. Acute perforation of the gallbladder into the free peritoneal cavity without protective adhesions.

To these types of perforation of the gallbladder may be added a fourth and rare type—perforation through the abdominal wall.⁶

The four types of perforation do not have the same danger potentialities. They may all add to the mortality rate of acute cholecystitis, although the mortality rate of the first and fourth groups may be far remote from the time of the attack of acute cholecystitis.

The incidence of perforation of the gallbladder as a complication of acute cholecystitis is uncommon and the incidence of perforation into the free peritoneal cavity is rare. In a review of 2,261 reported cases of acute cholecystitis Cowley and Harkins² found that the incidence of perforation of all types was 13 per cent. In a study of approximately 600 cases of acute cholecystitis Fletcher and Ravdin⁴ found 30 perforations. Only five of these perforations were into the free peritoneal cavity, an incidence of 0.8 per cent of the 600 cases. There was but one perforation into the free peritoneal cavity in our series of 75 cases of clinically acute cholecystitis, or an incidence of 1.3 per cent.

A diagnosis of acute cholecystitis with perforation may be very difficult. Mentzer (1932) mentions 4 patients who developed acute perforations—while under observation—which were not recognized before death. Judd and Phillips⁸ had a similar experience with 7 patients in whom they were not able to recognize symptoms of gallbladder disease. Each of these patient's necropsy revealed the cause of death as perforation of the gallbladder. Judd and Phillips also recorded 18 patients with acute cholecystic disease—found at necropsy—in which the gallbladder disease was not the cause of death. Wallace and Allen¹³ reported 44 cases of patients who were operated upon within four hours after admission to the hospital. There were 17 errors in diagnosis in this group. Eleven were operated upon for acute appendicitis and 6 for perforated peptic ulcer. These authors conclude that emergency operation for acute cholecystitis is not particularly hazardous, but remark that without an adequate operating room team, the operation is a poor one for the middle of the night. There were four deaths in the group of 44 patients having emergency operations. We have recently operated upon a patient (not included in the tables) who entered the hospital with a very acute abdominal condition. Almost every diagnosis—but the right one—was made by several members of our staff. At operation general peritonitis was found due to a gallbladder perforation into the free peritoneal cavity. A cholecystectomy was done and the patient recovered without complication. The experiences here recited emphasize that the diagnosis of acute cholecystitis, with or without perforation of the gallbladder, may—at times—be difficult or impossible.

Delay in operation has not increased the mortality rate in our series of patients with clinically acute cholecystitis. Our results do not agree with those reported by Wallace and Allen who recorded a mortality rate of 2.77 per cent when operation was done within four days or less after onset of symptoms; 6.78 per cent in five to eight days after onset; and 7.47 per cent nine or more days after onset. These authors state that from 4 to 12 days after the onset of acute cholecystitis is the most lethal period for operative treatment. Ross, Boggs and

Dunphy concurred in the opinion expressed by Wallace and Allen, but believed that the most lethal period is due to the increasing severity of the disease rather than to operation done during this period. These authors concluded that the concept that there is a critical period during which operation for acute cholecystitis is to be avoided should be abandoned.

CONCLUSIONS

From our small series of patients it is apparent that both early and delayed operations are satisfactory for the treatment of acute cholecystitis.

All patients with acute cholecystitis should be hospitalized promptly.

All patients with acute cholecystitis should be operated upon before they leave the hospital unless there is some definite contraindication to major surgery.

After years of doubt concerning early operation for acute cholecystitis by the senior author (T. G. O.), he has concluded that operation is indicated as soon as the patient can be prepared, providing the diagnosis is reasonably well established and there are no serious contraindications to operation.

Operation for symptomless gallstones is justified to prevent the increasing incidence of complications as the patient grows older.

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ATYPICAL APPENDICITIS

ITS PECULIAR PROBLEMS AND COMPLICATIONS

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The present day morbidity and mortality rate of acute appendicitis is chiefly related to unusual situations in which there is delay in diagnosis and treatment. For this reason certain categories of patients are considered as entities apart from the typical types of acute appendicitis.

Mestivier,¹⁶ in 1759, removed a pint of pus from the right iliac fossa. The patient died a few days later, and at necropsy a large rusty pin was found in the vermiform appendix. In 1824, Villarmy¹⁶ described some of the clinical symptoms of acute appendicitis as follows: "the earliest symptom appearing in the form of colic is probably accounted for by the inflammation and distention of the appendix. Its rupture occasioned an effusion which was responsible in turn for peritonitis." Melier,¹⁶ in 1827, wrote about acute disease of the appendix as a clinical entity which might, under certain circumstances, become a rapidly fatal disease. For some time these accurate opinions were smothered by prominent surgeons who adhered to the *typhlitis* explanation of disease in the right iliac fossa.

In the year 1848, Hancock¹⁶ of Charing Cross Hospital, successfully operated upon a diseased appendix before fluctuation occurred. Willard Parker,¹⁶ in 1850, published 4 case histories in which pus was evacuated successfully from the right iliac fossa. In 1856 Robertson¹⁵ reported 3 cases occurring in his practice over a 20 year period. All of his cases came to autopsy and the condition was attributed to perforation of the appendix. Lewis,¹³ in the same year reviewed the literature for acute diseases of the appendix and gave tables and statistics on 47 cases dating back as far as 1833. He found records of only 3 cases which recovered. He recommended incising the abdomen before fluctuation occurred. Following this report there was an era in which there was an occasional operation for acute appendicitis.

The epoch making account of Fitz⁸ in 1886, in which he collected and reported 100 cases of successful drainage of appendiceal abscess, started rapid advances in the next decade. Surgical opinion began to crystallize under the influence of Morton, Sands, McArthur, McBurney and Fowler. Fowler⁹ reported 200 cases of successful appendectomy in 1894. "The earlier the operation, the better," preached by Murphy was generally accepted. Ochsner and others advanced the knowledge of spreading peritonitis and its treatment. Currently, the advent of antibacterial agents has caused another advance in which there is a trend to operate upon all cases of appendicitis if possible.

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Mortality Rate of Appendicitis. Hoerr,¹⁰ in 1942, in a 25 year study covering 2,192 cases, found a mortality rate of 1.2 per cent in acute appendicitis. In acute appendicitis with perforation, the mortality rate was 17.1 per cent and in acute appendicitis with abscess formation, 7.3 per cent.

Stafford,¹⁸ of Johns Hopkins Hospital, in a survey made from 1931 to 1939 studied 479 cases of acute appendicitis with perforation. This number constituted one-third of the cases of acute appendicitis seen. Perforations occurred prior to entering the hospital in these 479 cases. There were 48 deaths in the group with perforations, a mortality rate of 10 per cent. Generalized peritonitis accounted for death in 13 patients. Inadequate treatment was considered the cause of death in 14 patients. Other causes of death were chiefly those incident to operation or to illness. Most of the patients having uncontrollable generalized peritonitis represented instances of delayed diagnosis and hospitalization.

In discussing factors contributing to the decrease in the mortality rate of acute appendicitis, authors are not in agreement on all points. Factors listed fairly consistently are:

1. Less delay in diagnosis.
 - a. Education of the laity.
 - b. Earlier consideration of the disease by the physician.
2. Advances in treatment of complications.
 - a. Gastrointestinal suction.
 - b. Increased use of parenteral supportive therapy.
 - c. Antibacterial drugs.

Although considered foremost by some, improved anesthesia, the McArthur-McBurney incision, and the decreased use of drains, appear to be relatively less important factors.

The following classification is presented to include the special categories of patients and the factors which contribute to atypical syndromes of appendicitis:

Patient Variants

- Infants
- The aged
- The obese

Anatomic Variants

- The retrocecal location of the appendix.
- The pelvic location of the appendix.
- The appendix contained in the hernial sac.
- Incomplete bowel rotation.

Concurrent With Other Conditions.

- Pregnancy, labor and puerperium.
- Postoperative convalescence.
- Acute infections elsewhere.

Acute Appendicitis in Infants. Acute appendicitis is not the most frequent cause of an acute condition in the abdomen in infants as it is in older children, and for this reason it often masquerades as gastro-enteritis or respiratory infection until perforation. Snyder and Chaffin¹⁷ collected cases reported under the age of 2

years and found that 71 per cent had perforated, and had peritonitis or an abscess by the time the diagnosis was made. In a study of 21 cases of their own series, they found that pain and tenderness are very difficult to interpret in infants and that localization is often impossible. Positive points which were considered adequate for diagnosis were:

1. Persistent vomiting.
2. Continued inability to nurse or take food.
3. Prolonged fretfulness.
4. Presence of constipation or diarrhea.
5. Temperature elevation.

In 67 per cent of Snyder and Chaffin's 21 cases the diagnosis was not made until three days after onset of symptoms or later.

*Collected series of cases of appendicitis in infants under 2 years of age**

<i>Author</i>	<i>Year</i>	<i>No. Cases</i>	<i>Mortality Per Cent</i>
Kelly	1923	5	—
Bolling	1924	8	37
Howland	1924	7	14
Christopher	1926	3	—
Farr	1928	9	22
Flusser	1933	6	33
Stone	1935	6	—
Potts	1938	18	—
Caldwell	1938	12	25
Edberg	1939	8	25
Hudson	1939	24	16
Alford	1941	16	—
Penberthy	1942	56	28
Anderson	1944	17	47
Scott	1945	23	13
Basch	1945	12	} 18
Basch	1945	5	
Caballero	1945	7	
Kirminsson	1945	26	54
Williams	1947	12	25
Greene	1949	9	44
McLanahan	1950	4	0
Abel & Allen	1950	24	41
Morton	1950	2	0
Snyder & Chaffin	1951	21	19
Benson	1951	43	13.9
Single case reports†	—	39	36
Heyl	—	9	33
Total cases		431	
Total cases quoting mortality		366	25.7

* William H. Snyder, Jr., and Lawrence Chaffin. Appendicitis During First Two Years of Life. *Arch. Surg.* 64: 551, 1952.

† Idem, *ibid.*

Benson, and associates,¹ studied 41 cases of acute appendicitis in infants under 24 months of age and found 33.3 per cent with perforations and 48.7 per cent with abscesses. He attributes the frequent development of peritonitis before diagnosis to the following factors:

1. The use of cathartics for upset stomach.
2. Inability of infants to express themselves or to localize the complaints.
3. Inability of the underdeveloped omentum to assume its protective role.
4. Retention by cecum in a high position.

Benson advises repeated examinations at short intervals under barbiturate sedation if necessary. He concluded that, although little progress has been made in reducing the incidence of peritonitis in infants, there has been great advancement in its treatment.

Acute Retrocecal Appendicitis. Stalker,¹⁹ in considering acute retrocecal appendicitis, stressed the frequency of atypical signs and symptoms and the unrecognized course of the disease. Collins⁴ reported 751 instances of acute retrocecal appendicitis in 3,003 consecutive appendectomies for acute appendicitis, and he likewise emphasized the frequent bizarre nature of the early signs and symptoms. Collins considered 25 per cent of all cases of appendicitis to be anatomically retrocecal. In 56.9 per cent, these cases had previously been diagnosed as diseases of the gallbladder, pyloric region, pelvis, and right genito-urinary system. As a result of these errors in diagnosis in this series the correct diagnosis was made in only 40 per cent of the cases. There were 58 deaths, a mortality rate of 7.7 per cent.

Nonlocalization. Nonlocalization of the signs and symptoms as a chief cause of delay in the diagnosis of acute appendicitis has been studied by Keyes.¹¹ He proposes reversing the emphasis in these cases from the physical signs to the history. In 16 cases of nonlocalization in 145 consecutive cases of acute appendicitis, there was a characteristic history as follows:

1. Pain beginning in the midline and persisting for eight hours or more.
2. Anorexia and an urge to defecate.

These symptoms were present in 88 per cent of those patients who had nonlocalization.

Appendicitis and Pregnancy. Because of certain confusing features, acute appendicitis, particularly with perforation, is a serious problem during pregnancy. As the pregnancy advances the mortality rate increases and the lives of both the mother and the child are endangered.

Fueth,¹⁴ in 1905, called attention to the anatomic displacement of the cecum and the appendix by the enlarging uterus of pregnancy. Other authors^{6, 7} have pointed out other anatomic and physiologic factors contributing to the atypical syndromes and delay in diagnosis of acute appendicitis during pregnancy as follows:

1. Because of the upward displacement of the appendix, suppuration, when it occurs, involves the higher and less resistant portions of the peritoneum.
2. Because the uterus occupies the greater part of the abdominal cavity, drainage of pus tends to spread.

The diagnosis is also confused by certain symptoms common in both pregnancy and appendicitis:

1. Nausea.
2. Pain in the abdomen.
3. Physiologic leukocytosis of pregnancy.
4. Right sided pyelitis.

Atypical physical signs which occur are:

1. Because of the physiologic distention of the abdominal wall, muscle rigidity may be absent.
2. Rebound tenderness is less frequent.
3. Psoas spasm and McBurney point tenderness may be absent for anatomic reasons.
4. Rectal examination may not reach the tenderness.

Krieg¹² studied 200 cases of acute appendicitis in pregnancy and found that the usual physical signs were poorly demonstrable or absent in about 50 per cent of the cases. He concluded that the history of acute appendicitis in the pregnant patient was the same as that in any other person, and is the most reliable feature in the diagnosis. The deaths in the series were found in the well advanced cases of appendicitis and peritonitis.

The treatment during the first seven months of pregnancy is appendectomy. During the last two months cesarian section, preferably extraperitoneal, and appendectomy through a high incision is recommended.

Appendicitis in the Aged. In the aged there is a tendency toward atypical symptomatology of appendicitis. They seek medical aid late, a correct diagnosis may be difficult, and perforation and diffuse peritonitis occur frequently. Boyce,² summed up the clinical problem thus: "Acute appendicitis in the aged can justifiably be regarded as a special disease."

Collins⁵ found, in a survey of 12,813 consecutive cases of acute appendicitis, 97 deaths, or a mortality rate of 0.76 per cent. There were 58 deaths in 529 patients of this series who were aged 40 and older, a mortality rate of 10.96 per cent. Collins stated that failure to make a correct diagnosis of appendicitis in patients over 40 years of age, is frequently followed by death of the patient. In case of doubt as to the presence of appendicitis the iliocecal region should be explored.

Burnett³ reviewed 197 cases of perforation due to appendicitis, found over a nine year period at the Oklahoma University Hospitals prior to April 1948. The mortality rate for the 147 cases operated upon was 8.1 per cent as opposed to a 14.0 per cent mortality rate for those treated conservatively. From a review of 49 additional cases of perforated appendicitis in this hospital, the following representative cases are cited.

CASE REPORTS

Case 1. Mr. J. S. (Oklahoma University Hospital), aged 80, was admitted on May 14, 1950 complaining of abdominal pain and vomiting. The illness began four days before admission with generalized upper abdominal pain without nausea. Constipation ensued and was treated by mineral oil and an enema. Pain moved to the right lower abdomen and

vomiting began on the day before entering the hospital. On examination the patient did not appear to be ill. The temperature was normal. There was localized tenderness over McBurney's point. Leukocytosis was 21,000 per cu. mm. At operation a well localized pericecal abscess was found containing thick pus and a perforated appendix. The postoperative course was complicated by an abscess in the incision resulting in a hernia which was repaired at a second operation two months later.

Comment: This case illustrates a common situation in the aged. The patient delayed 24 hours before calling a physician because he was not very ill. The physician watched him through another 48 hours, probably due to lack of nausea and vomiting, or localizing physical signs. Because of the delay in treatment avoidable complications arose. An abscess developed in the incision and finally another operation was necessary to repair a hernia.

Case 2. Baby L. B. aged 18 months (Children's Hospital) entered the hospital April 22, 1952 with a tentative diagnosis of acute intestinal obstruction. There was a history of undiagnosed abdominal distention and vomiting at two months of age. The present illness began with vomiting three days before admission. After 24 hours the patient was holding the abdomen and crying. Abdominal distention developed soon afterward. Examination on the third day showed dehydration, a fever of 101 F., pulse rate 120, marked abdominal distention, generalized tenderness and absent peristalsis. There was little change in the leukocyte count. The preoperative diagnosis of intestinal obstruction was confirmed at operation and found to be caused by a loop of small bowel caught in an opening beneath the appendix. The tip of the appendix was adherent to the ileum where a fistula had formed between the appendix and the ileum. The patient recovered.

Comment: In this infant, it is surmised that an episode of acute appendicitis perforated into the ileum at 2 months of age and was the cause of intestinal obstruction 16 months later.

Case 3. Mr. F. M. aged 68 (University Oklahoma Hospital) entered the hospital July 9, 1952 complaining of abdominal pain. The tentative diagnosis was carcinoma of the cecum. He had been hospitalized for 10 days a year ago for abdominal pain without nausea or vomiting. He noted a mass in the right lower abdomen four months ago. He had lost 30 pounds in weight. At operation for an undiagnosed mass he was found to have an old perforated appendix and a cecum just under the margin of the liver. He recovered.

Comment: The symptoms at the onset were not recognized as due to appendicitis. The appendix and cecum were high. After the acute process subsided the residual mass was suspected of being malignant.

SUMMARY

In reviewing reported series of acute appendicitis, the morbidity and mortality rates related to delay in diagnosis is emphasized. Atypical syndromes have been discussed in relation to special categories of patients. Three representative case reports have been presented.

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CHRONIC NEUTROPENIA: REPORT OF FIVE CASES TREATED BY SPLENECTOMY

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Chronic neutropenia presents many diagnostic problems and classification of cases is made difficult by considerable overlapping in the clinical manifestations of the various syndromes associated with a low leukocyte count. Correct diagnosis is very important in cases of neutropenia, since the value of splenectomy in many of the neutropenic syndromes has been adequately demonstrated. In primary splenic neutropenia, splenectomy, according to the majority of the reports, appears to be curative.^{10, 11, 12, 17, 19, 20, 23, 25} The same procedure is of benefit in cases of neutropenia associated with splenic panhematopenia.² The neutropenia observed in atrophic arthritis with splenomegaly (Feltz's syndrome)³ may be improved by removal of the spleen.^{1, 5, 7, 8, 9, 18} Recently Spaet and Dameshek²¹ have recorded 4 cases of chronic hypoplastic neutropenia in which the neutropenia observed was not affected by splenectomy. The reports of cyclic neutropenia treated by splenectomy are few and the results are variable.^{4, 13, 16}

It is the purpose of this report to record 5 cases in which chronic neutropenia was treated by splenectomy with variable results. The difficulties encountered in diagnosis of the various neutropenic syndromes are enhanced by the considerable degree of overlapping between the individual syndromes. In 3 of the cases in this report, diagnosed respectively as cyclic neutropenia, splenic panhematopenia and Feltz's syndrome, the response to splenectomy revealed varying degrees of benefit. The fourth case in this report has been recorded in detail previously¹⁸, but is included in order to record the results of subsequent necropsy. The fifth case was unaffected by splenectomy and is a probable example of chronic hypoplastic neutropenia.

CASE REPORTS

Case 1. Periodic Cyclic Neutropenia Treated by Splenectomy. The patient was a white woman aged 72 at the time of the first examination by one of us (H. M. R.) in December 1948. The major complaints at the time of examination were weakness, fever and recurrent skin infections. For two years previously she had known of a low leukocyte count at varying intervals. Several blood transfusions had resulted in only transitory improvement, and medications consisting of crude liver extracts, iron and folic acid had been ineffective in elevating the leukocyte count. There had been no loss of weight, abnormal bleeding tendencies, jaundice or arthritis. There was no history of exposure to injurious chemicals or medications. The pulse rate was 72 beats per minute. The blood pressure was recorded as 140 mm. of mercury systolic and 80 diastolic. No enlarged lymph nodes were observed. The abdominal examination did not demonstrate enlargement of the liver or the spleen. No joint manifestations were present.

The preoperative studies of the blood are given in table 1. In addition urinalysis, icterus index and erythrocyte fragility tests were recorded as normal. Sternal bone marrow

aspiration revealed no defect in the maturation of leukocytes and erythropoiesis was normal. A differential count of 100 nucleated cells is tabulated as follows:

<i>Differential</i>	
Polymorphonuclear cells	45%
Metamyelocytes	10%
Myelocytes	19%
Premyelocytes	5%
Myeloblasts	1%
Lymphocytes	9%
Megaloblasts	1%
Normoblasts	10%
100 cells	

TABLE 1
Preoperative blood studies (Case 1)

Date	Leukocytes per cu. mm. of blood	Erythrocytes, millions per cu. mm. of blood	Hemo- globin, per cent	Leukocytes, per cent						
				Segmented poly- morpho- nuclears	Stab forms	Juве- nile	Lympho- cytes	Mono- cytes	Baso- phils	Eosin- ophils
6/13/46	2,000	3.88	79	60			not reported			
9/9/46	2,500			4						
9/12/46	1,500			24						
10/21/46	950			28						
11/26/46	2,850			10						
2/4/47	950			7						
3/12/47	2,700			2						
1/2/49	3,900	3.97	74	10	8	4	66	12	0	0
1/22/49	3,650			12	10	5	67	6	0	0
1/25/49	4,850	4.84	96	23	5	5	61	6		

The thrombocytic elements were present in normal numbers and young forms of granulocytes were present in somewhat greater than normal numbers. There was no evidence of leukemia or metastatic malignant lesions. The coagulation and bleeding times were normal. The platelet count was 243,000 per cu. mm. of blood.

Splenectomy was done (P. D.) on Jan. 28, 1949. No accessory spleens were found. The spleen, which weighed 96 Gm. and measured 10 cm. by 6 cm., appeared normal. Histologic examination showed an increased prominence of the stroma between the sinuses. In these areas there was increased deposition of intracellular and extracellular hemosiderin. The histologic picture was similar to that observed in a spleen where there was excessive breakdown of erythrocytes. Supravital stains were not made, but phagocytosis of granulocytes by the reticuloendothelial system was not observed histologically.

The patient's postoperative course was uneventful. In May 1949, she returned to her home in New Jersey. Subsequent reports were obtained from her physician in Dover, New Jersey, with the last report dated Dec. 3, 1951. During the postsplenectomy period there had been no return of fever and on only one occasion was there a slight return of localized skin infection. A certain degree of lassitude and fatigue has persisted, but with this exception the patient has remained in good health. Low polymorphonuclear leukocyte counts

were obtained during a portion of the postoperative period, but for the most part the total leukocyte count was definitely elevated to within normal limits (table 2).

Comment: This case is considered as one of periodic cyclic neutropenia¹⁵ in view of the absence of splenomegaly. If enlargement of the spleen had been present all of the charac-

TABLE 2
Postoperative blood studies (Case 1)

Date	Leukocytes per cu. mm. of blood	Erythrocytes, millions per cu. mm. of blood	Hemo- globin, per cent	Leukocytes, per cent							
				Segmented poly- morpho- nuclears	Stab forms	Juve- nile	Lym- pho- cytes	Mono- cytes	Baso- phils	Eosin- ophils	Myc- elo- cytes
1/28/49, Splenectomy. 500 cc. blood transfusion during operation											
1:00 P.M.	21,000	5.1	109	29	44	6	20	1			
2:00 P.M.	21,200			48	37	5	10	0			
3:00 P.M.	34,500			37	54	3	6	0			
4:00 P.M.	38,900			44	47	3	5	1			
1/29/49	23,000			26	65	0	8	1			
1/30/49	16,100			62	22	4	12	0			
1/31/49	17,400			70	12	3	15	0			
2/10/49	8,200			61	11	3	25	0			
2/15/49	5,100	4.47	86	27	12	3	50	7		1	
3/1/49	6,600	4.55	93	54	5		38	3			
3/8/49	6,400	4.81	93	17	3	3	71	6			
3/15/49	7,000	4.86	102	20	1	1	78				
3/22/49	5,400	4.56	86	11	4		84	1			
3/29/49	9,800	4.94	89	12	2	2	81	3			
4/5/49	7,900	4.19	83	18		2	79	1			
4/12/49	7,600	4.53	95	23	10		64	3			
4/19/49	7,900	4.47	83	28	2		66	4			
4/26/49	7,200	4.09	89	17	4		76	3			
5/3/49	5,600	4.39	86	5			94	1			
5/10/49	4,000	4.04	80		2		96	2			
5/17/49	5,700	4.00	80	10	5	1	84				
5/24/49	4,300	4.06	83	21		1	77			1	
1/20/50	5,300	3.82	72	44			54	2			
3/10/50	3,400	3.86	76	4			94	2			
6/26/50	4,000	3.58	70	46			53	1			
7/24/50	5,800	4.2	78	34			60	6			
10/18/50	4,750	4.4	81	30			68	2			
11/28/50	4,600	4.1	82	38			62	0			
1/3/51	5,200	3.9	73	26			73	1			
2/26/51	4,000	3.38	70	26			73	1			
3/31/51	4,600	3.8	74	21			79				
4/9/51	5,300	3.94	84	37			63				
5/5/51	5,000	3.92	72	36			61	2			

teristics of primary splenic neutropenia as stipulated by Wiseman and Doan²⁵ would have been fulfilled. Objective improvement, in respect to freedom from recurring fever and infections, was accomplished by splenectomy. While the percentage of polymorphonuclear leukocytes was not increased as much as was the total number of leukocytes, the total

number of circulating polymorphonuclear leukocytes was definitely improved by splenectomy. However, the hematologic response in this case was not so great as in those cases of splenic neutropenia with splenic enlargement.

Case 2. Splenic Panhematopenia Treated by Splenectomy. The patient was a white woman aged 41 at the time of first examination on May 31, 1951. The chief complaints were fatigue, weakness and loss of weight, (10 pounds), during the preceding three years. Several periods of hospitalization had been previously necessitated because of pyelitis, during which time anemia and neutropenia were observed. Twelve weeks prior to the first examination enlargement of the spleen had been observed. The results of physical examination, with the exception of splenomegaly, were noncontributory.

The average of three peripheral blood counts prior to splenectomy gave the following results: leukocytes 2,800 per cu. mm. of blood, erythrocytes 4,300,000 per cu. mm. of blood and hemoglobin determination 86 per cent. The differential leukocyte percentage for those counts was polymorphonuclear leukocytes 54, nonsegmented leukocytes 4, metamyelocytes 2, eosinophils 2, lymphocytes 38. The platelet count was 73,000 per cu. mm. of blood. The following additional laboratory work was done. The Kahn flocculation reaction for syphilis was negative. The erythrocyte sedimentation rate by the Wintrobe method was 42 mm. in one hour. The icterus index was 7 units. The cephalin flocculation reaction was 2.5. The sulfobromophthalein reaction was normal. The Congo red test revealed 18 per cent absorption. The erythrocyte fragility test revealed initial hemolysis at 0.44 and complete hemolysis at 0.32 which was identical with the control. The total protein was 6.4 Gm. per 100 cc. of whole blood. The serum albumin was 4.7 Gm. and the serum globulin was 1.7 Gm. The A-G ratio was 2.7:1. The prothrombin time was 18.5 seconds compared with a control of 17.0 seconds. The urea nitrogen was 10 mg. per 100 cc. of whole blood. The results of urinalysis were normal. Intravenous pyelographic studies were normal. Peripheral blood smears for malarial parasites were negative.

Aspiration of sternal marrow revealed the following percentages for 100 nucleated cells

Myeloblasts	3%
Premyelocytes	8%
Myelocytes	25%
Stabs (P.M.N.)	14%
Segmented P.M.N.	14%
Lymphocytes	5%
Microblasts	3%
Erythroblasts	6%
Normoblasts	22%

100 cells

Liver biopsy done on June 3, 1951, showed no evidence of cirrhosis, malignancy or active viral hepatitis. Roentgenographic examinations of the chest and gastrointestinal tract were recorded as normal. Stool examination was negative for blood, ova and parasites.

On Aug. 18, 1951, splenectomy was done. The spleen, which was enlarged, weighed 366 Gm. The liver, pancreas, stomach, duodenum, gallbladder and colon were negative. No varices of the portal system were observed and no accessory spleens were found.

Histologic examination of the spleen revealed dilatation of the splenic sinuses. These sinuses were not congested, but their walls were slightly thickened. The endothelioid cells were swollen. Eosinophilic leukocytes appeared to be increased and there was slight increase of connective tissue. The malpighian corpuscles were less numerous than normal, and some showed active lymphopoietic function. The histologic picture was consistent with splenic pancytopenia.

The patient's postoperative course was uneventful. The results of postoperative studies of the peripheral blood were as follows. The average of six blood counts was 12,100 leuko-

cytes per cu. mm. of blood, 4,900,000 erythrocytes per cu. mm. of blood and hemoglobin 90 per cent. The average leukocyte percentage for these blood counts was polymorphonuclear leukocytes 69, nonsegmented leukocytes 6, myelocytes 2, eosinophils 3, and lymphocytes 20. The platelet count on Aug. 19, 1951, was 74,000 per cu. mm. of blood and on November 15, 382,000 per cu. mm. of blood. The patient has been seen at regular intervals since the operation. An adequate erythrocyte and leukocyte count has been maintained. No further infections of the urinary tract have been present and she has been relieved of her weakness and fatigue.

Comment: This case is best classified as splenic panhematopenia. Preoperatively there was lowering of erythrocytes, platelets and to a lesser extent the polymorphonuclear leukocytes. After splenectomy all of the elements formed in the marrow were definitely improved and normal peripheral blood counts were obtained at all times.

Case 3. Splenomegaly Associated With Neutropenia, Atrophic Arthritis (Felt's Syndrome) and Amyloid Changes, Treated by Splenectomy. The patient was a white man aged

TABLE 3
Preoperative blood studies (Case 3)

Date	Leukocytes per cu. mm. of blood	Erythro- cytes, millions per cu. mm. of blood	Hemo- globin, per cent	Leukocytes, per cent						
				Segmented polymorpho- nuclears	Stab forms	Juве- nile forms	Lym- pho- cytes	Eosin- ophils	Baso- phils	Mono cytes
1/16/48	2,250	5.15	90	43	20		35	2		
1/20/48	2,400	3.95	79	52	5		40	1	1	1
1/24/48	1,050			68	6		24	2		
1/26/48	1,800			68	15		17			
11/4/48	2,400	3.62	59	64	15	1	20			
11/6/48	3,500	4.23	59	54	21		25			
11/14/48	2,700	4.11	61	56	22		22			
12/3/48	2,950	4.15	57	58	8		30	4		
12/19/48	3,350	4.62	63	58	5		30	7		
1/7/49	4,750	4.03	58	58			41	1		
1/20/49	1,850	3.24	52	61	2		33	4		
4/27/49	2,000	3.59	58	56			42	2		
5/2/49	2,200	3.98	65	50	2		48			
5/14/49	1,500	3.73	65	47	3		50			

62 at the time of his first examination on Jan. 19, 1948. He was hospitalized for urinary symptoms that were the result of benign prostatic hypertrophy. At this time neutropenia was observed. The past medical history revealed that for 20 years the patient had been troubled with recurring episodes of joint pain, involving the fingers and bones. He had been aware of a heart murmur for many years. Moderate fatigue was also present.

The physical examination did not reveal evidence of pain, cyanosis or dyspnea. No enlargement of lymph nodes was present. There was a mitral systolic murmur, grade 2. The blood pressure was 140 mm. of mercury systolic and 80 diastolic. The abdominal examination did not reveal splenic or hepatic enlargement. Rheumatoid changes were present in the fingers and in the feet.

The results of examination of the peripheral blood prior to splenectomy are given in table 3. The urine was negative. The nonprotein nitrogen was 35 mg. per 100 cc. of whole blood and the blood sugar was 118 mg. per 100 cc. of whole blood. The serum protein was 9.2 Gm. per 100 cc. of whole blood. The sedimentation rate was 24 mm. in one hour. Urine examination for Bence Jones protein was negative. The electrocardiogram was interpreted as being within normal limits.

Sternal aspiration revealed normal erythropoiesis and adequate numbers of megakaryocytes. The myelocytic cells appeared to be increased in number. No myeloma cells were observed. A tentative diagnosis of hypersplenism and Felty's syndrome was made. In view of the absence of demonstrable splenomegaly, splenectomy was not suggested at this time. Rheumatic heart disease with mitral regurgitation was present.

On Nov. 3, 1948, the patient was readmitted for a rectal abscess. He received four transfusions during this period of hospitalization. The rectal abscess was treated surgically without any complications. The urine examination at this time revealed a trace of albumin.

On April 25, 1949, the patient was readmitted to the hospital because of progressive neutropenia, increased weakness, exhaustion and fatigue. For six weeks prior to this examination moderate ankle edema had been observed. There had also been increased pain and swelling of the hands, wrists and fingers. The following pertinent changes in the physical examination were present. The spleen was palpable 1 to 2 fingerbreadths below the left costal margin. Ankle edema of moderate degree was present.

The following laboratory work was done. The urine examination now revealed a specific gravity of 1.012. The albumin reaction was grade 4. The sugar determination was negative.

TABLE 4
Postoperative blood studies (Case 3)

Date, 1949	Leukocytes per cu. mm. of blood	Erythro- cytes, millions per cu. mm. of blood	Hemo- globin, per cent	Leukocytes, per cent				
				Segmented poly- morpho- nuclears	Stab forms	Lympho- cytes	Baso- phils	Eosino- phils
5/18 (1:45 P.M.)	4,000	4.2	81	81		19		
5/18 (4:00 P.M.)	4,800	4.26	77	72	12	16		
5/19	4,900	4.28	77	78		22		
5/21	4,900	4.27	81	83		15	1	1
5/23	7,850	5.16	84	76	1	20	1	2
5/28	9,150	4.49	84	89		10		1
6/2	9,550	4.27	84	89		8		3
6/6	12,500	4.32	84	96		4		

The microscopic examination was negative. The clotting time was 3 minutes, 25 seconds and the bleeding time was 2 minutes. The erythrocyte fragility test revealed beginning hemolysis at 0.42 per cent and complete at 0.28 per cent. The control test showed beginning hemolysis at 0.42 per cent and complete at 0.28 per cent. The Kahn reaction was negative. The non-protein nitrogen was 35 mg. per 100 cc. of whole blood. The phenolsulfonphthalein test revealed 7.5 per cent excretion in one hour, 5 per cent excretion during the second hour and 7.5 per cent excretion during the third hour, or a total of 20 per cent excretion in three hours. The electrocardiogram was unchanged. The A-G ratio was 1.59:1.

In view of the persistent neutropenia and weakness splenectomy was done on May 18, 1949. The spleen weighed 1,258 Gm. The histologic examination revealed large pink-staining areas that replaced many of the malpighian corpuscles. Some of the smaller blood vessels also had a homogeneous pink appearance in the media. There were increased numbers of plasma cells. Amyloid stains were positive. The histologic diagnosis was secondary amyloidosis of the spleen.

The results of postoperative blood counts are given in table 4. The patient did well until June 5, at which time there developed circulatory collapse. Death occurred the next day. Permission for necropsy was refused.

Comment: This case had the clinical features of Felty's syndrome with atrophic arthritis, neutropenia and splenomegaly. Amyloid changes developed as the result of long-standing infection. It is probable that associated amyloidosis of the kidneys was also present although necropsy studies were not obtained.

Case 4. Neutropenia Associated With Felty's Syndrome. This case has been reported previously by Rogers and Langley.¹⁸ Since this report, death has occurred and necropsy studies have been made. In view of the paucity of necropsy studies in cases of hypersplenism this report is made.

The patient maintained a relatively good state of health until July 13, 1950. Peripheral blood studies showed the leukocyte count to be well maintained and the differential count showed adequate levels of polymorphonuclear leukocytes. In July, however, an unexplained constipation developed, associated with some distress in the right side of the abdomen. Roentgenographic studies revealed carcinoma of the ascending colon. Spider angiomas were also demonstrated.

At this time the following laboratory work was done. The serum protein was 6.8 Gm. per 100 cc. There was a reversal of the A-G ratio, concentration of the albumin being 2.99 Gm. and the globulin 3.81 Gm. per 100 cc. The cholesterol was 109 Gm. per 100 cc. The prothrom-

TABLE 5
Blood studies (Case 4)

Date, 1950	Leukocytes per cu. mm. of blood	Erythro- cytes, millions per cu. mm. of blood	Hemo- globin, per cent	Leukocytes, per cent					
				Segmented polymorpho- nuclears	Stab forms	Lympho- cytes	Mono- cytes	Eosin- ophils	Baso- phils
5/3	6,100	5.38	99	47		44	2	7	
7/11	6,150	4.79	94	49	3	46	2		
7/27	9,400	3.46	71	66	3	30			1
7/29	5,750	4.01	79	57	7	30	3	3	
11/1	6,500	4.16	84	37	8	48	3	3	1
12/8	3,400	4.76	96	12	13	71	2		2
12/11	6,500	4.08	81	60	9	26	4		1

bin time was 16 seconds compared with a control of 13 seconds. The blood sugar was 130 mg. per 100 cc. of whole blood.

On July 22, 1950, an obstructing carcinoma of the ascending colon was removed. Histologic examination revealed an adenocarcinoma, grade 2 to grade 3. During the next five months the patient showed increasing evidence of hepatic damage, with icterus, increased serum protein and progressive elevation of serum globulin to 6.41 Gm. per 100 cc. There was increasing abdominal pain. Death occurred on Dec. 29, 1950, as a result of metastases from carcinoma of the ascending colon. The results of all unreported peripheral blood studies are included in the table 5.

At necropsy the following pertinent anatomic diagnoses were made: cirrhosis of the liver, metastatic carcinoma of the liver (secondary to carcinoma of the colon), thrombosis of portal vein, secondary to neoplasm, metastatic carcinoma of the diaphragm and mesentery, bilateral bronchopneumonia and coronary arteriosclerosis, grade 2.

The liver was nodular with superimposed nodules measuring 1 to 10 mm. in diameter. The portal vein was dilated, measuring 2.5 cm. at the entrance into the liver. Old and recent thrombi were present, extending downward into the mesenteric and splenic veins. The thrombi contained microscopic evidence of tumor tissue.

Histologic examination of the lungs revealed bronchopneumonia. Several of the pulmonary arteries contained tumor thrombi. The liver revealed a Laennec type of cirrhosis

with fibroblastic proliferation of bile ducts, lobular distortion and lymphocytic infiltration. There were areas of necrosis of the hepatic cells and occasional areas of regeneration. The sinusoids were dilated and engorged, and the Kupffer cells contained a large quantity of yellow-staining pigment. Many areas revealed invasion of a well differentiated tumor, apparently of gastrointestinal origin. The interlobular veins contained thrombi, and the portal veins revealed tumor thrombi.

Sections of the pancreas revealed replacement of parenchyma by adipose connective tissue. The islets appeared normal.

Paraffin prepared sections of bone marrow revealed a normal marrow pattern, without evidence of tumor infiltration. Erythropoiesis and myeloid development were active, but megakaryocytes appeared reduced in numbers. Lymph nodes of the mesentery either were necrotic or revealed infiltration with neoplasm so that the presence or absence of increased reticuloendothelial activity could not be determined.

Case 5. Neutropenia Associated With Hookworm Infestation, Hyperplastic Bone Marrow Without Splenomegaly. Splenectomy, No Improvement and Subsequent Development of Hypoplastic Bone Marrow. The patient was a white man aged 24, who was examined in consultation by one of us (H. M. R.) at Bay Pines, U. S. Veterans Administration Hospital, on June 12, 1951. The presenting complaints were weakness, *blackout* spells and nose bleeding. There was a past history of mental deficiency and schizoid personality changes.

The physical examination revealed a well-developed, poorly nourished, chronically ill white man. The conjunctivae were pale. There was a small area of ecchymosis, measuring 3 mm., on the soft palate. There were a few small telangiectases on the chest. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The liver and spleen were not palpable.

The admitting blood count was erythrocytes 1,980,000 per cu. mm. with 42 per cent hemoglobin. The leukocyte count was 3,500 per cu. mm. with 46 per cent polymorphonuclear cells, 52 per cent lymphocytes and 2 per cent eosinophils. The reticulocyte count was 1 per cent. The prothrombin time was 13 seconds with a control of 12 seconds. The serologic reaction for syphilis was negative. The result of the stool examination was positive for hookworm ova and blood. Roentgenograms of the thorax were negative.

The patient's hookworm infestation was treated with tetrachlorethylene, and subsequent stools were negative for hookworm ova. By July 12, the erythrocyte count had risen to 4,300,000 per cu. mm. of blood.

The patient's course in the hospital was complicated by anemia and thrombocytopenia. Four platelet counts ranged from 30,100 to 38,000 per cu. mm. The leukocyte count ranged from 1500 to 3,800 per cu. mm. with polymorphonuclear cells averaging 30 to 48 per 100 cells. The serum protein was 6.4 mg. per 100 cc. of whole blood with a normal A-G ratio. Aspiration of sternal marrow showed normal maturation of leukocytes and erythrocytes and was more hyperplastic than normal. In view of the persistent neutropenia and thrombocytopenia splenectomy was done on Sept. 4, 1951.

The spleen, which weighed 85 Gm., was removed without complication. The histologic examination showed no evidence of excessive phagocytosis of leukocytes or erythrocytes. The peripheral blood studies in the immediate postoperative period revealed the erythrocytes to range from 4,200,000 to 4,300,000 per cu. mm. and the leukocytes from 3,000 to 4,000. The platelet counts averaged 16,000 to 20,000. Repeated stool examinations were negative for hookworm ova. Satisfactory response to splenectomy was not obtained. There were no hemorrhagic manifestations in spite of the low platelet counts.

The patient was re-examined on Feb. 21, 1952. Since previous discharge no hemorrhagic manifestations had been observed and there were no new symptoms of note. The results of physical examination were unchanged. The leukocyte count was 4,400 per cu. mm. There were 33 per cent polymorphonuclear cells, 11 per cent band forms, 1 per cent juvenile, 1 per cent eosinophils and 52 per cent lymphocytes. The platelet count was 24,480 per cu. mm.

The erythrocyte count was 2,040,000 per cu. mm. The stool examination was negative for blood, parasites and ova. The cholesterol was 260 mg. per 100 cc. of whole blood. The erythro-

cyte fragility test was within normal limits. The blood urea nitrogen was 16.5 mg. per 100 cc. whole blood. The serum bilirubin was 0.6 mg. The bleeding time was $3\frac{1}{2}$ minutes and the clotting time was 6 minutes.

Roentgenographic examinations of the skull, pelvis, humeri and femora were negative. At this time re-examination of the sternal marrow was made. This showed marked depression of the granulocytic series. There was quantitatively good erythroid reaction with prevalence of metachromatic normoblasts. Megakaryocytes were not observed. A biopsy from the upper end of the tibia showed extreme hypoplasia of the marrow without change in the bone framework.

The patient was given crude liver extract and vitamin B₁₂ parenterally. The maximal reticulocyte count was 6.1 per cent. On April 29, 1952, the blood count showed leukocytes 3,500 per cu. mm. and erythrocytes 2,010,000 per cu. mm. The differential count was polymorphonuclear leukocytes 40 per cent, band forms 2 per cent, eosinophils 2 per cent and lymphocytes 56 per cent. No benefit was obtained by splenectomy.

Comment: The case under discussion was first considered to be one of hypersplenism, but splenectomy did not benefit this patient. The absence of splenomegaly, both clinically and at the time of operation, is against this diagnosis. The change in the bone marrow pattern from hyperplasia to hypoplasia is of interest. In retrospect this case presents many of the characteristics of chronic hypoplastic neutropenia recently described by Spaet and Dameshek. In this case the degree of thrombocytopenia is more profound than in the cases recorded by Spaet and Dameshek.

DISCUSSION

In this report 5 cases of chronic neutropenia, in 4 of which there was clinical evidence of hypersplenism, and in which splenectomy was done, are recorded. In 3 of these cases distinct benefit, both hematologic and clinical, was obtained by this procedure. In 1 of these cases benefiting hematologically, death occurred as a result of underlying rheumatic heart disease and probable systemic amyloidosis. In this case the histologic examination of the spleen revealed widespread deposition of amyloid. It is probable that splenectomy at an earlier date might have altered the outcome. The fourth case of this report is 1 which has been reported previously but was included in this analysis because death had occurred and necropsy examination was obtained. Cases of hypersplenism with necropsy findings are relatively rare as demonstrated by the recent case report of Wiard and Robbins.²⁴ The fifth case is probably representative of chronic hypoplastic neutropenia. Hookworm infestation, which had been adequately treated, was observed in this case. The role of the parasitic infection cannot be evaluated. No benefit was obtained from splenectomy, and subsequent bone marrow examination revealed a change from an active marrow prior to splenectomy to a hypoplastic marrow after splenectomy. Two cases in this report were characterized by atrophic arthritis, splenomegaly and neutropenia (Felty's syndrome). One of these, previously reported by one of the authors (H. M. R.), stressed the beneficial effect of splenectomy in this syndrome. Since this report was submitted additional cases of Felty's syndrome have been reported in the literature in which beneficial effects were obtained by splenectomy. These reports include 2 cases of Smith and McCabe²⁰, 2 cases of Kanar and co-workers⁵, 1 case of Gauld⁵, 1 case of Kissmeyer-Nielsen⁹, 1 case of Hutt, Richardson and Stauffurth,⁷ Bauer and McDuffie¹ reported 1 case in which Felty's syndrome was treated by splenectomy, overlooked by this author in the previous report.

The classification in any case of chronic recurring neutropenia is at times difficult because of the overlapping of the clinical manifestations in the various syndromes. If there is neutropenia, without appreciable anemia or thrombocytopenia, associated with splenomegaly and a hyperplastic bone marrow, the diagnosis of primary splenic neutropenia is apparently in order. In a previous report⁸ comment was made on the similarity between chronic splenic neutropenia and Felty's syndrome. The only major differential points are arthritis occurring constantly in Felty's syndrome and an occasional case of Felty's syndrome existing with a hypoplastic marrow^{18, 20} instead of the hyperplastic marrow in primary splenic neutropenia. Some cases of primary splenic neutropenia have show joint manifestations and some have rheumatoid arthritis. The question then arises as to when they should be classified as Felty's syndrome (atrophic arthritis, neutropenia and splenomegaly). Smith and McCabe's²⁰ cases were reported as *primary splenic neutropenia with arthritis (so-called Felty's syndrome)*. Other cases of chronic cyclic neutropenia and recurring fever with occasional joint pains and no splenomegaly are classified as cyclic periodic neutropenia.¹⁵ Splenic panhematopenia differs from primary splenic neutropenia in that there are anemia and thrombocytopenia in the cases of panhematopenia.

It is apparent that there is considerable overlapping of these four syndromes, and this is further emphasized by the reports in the literature of cases in which neutropenia has been treated by splenectomy. In the case of cyclic neutropenia reported by Reznikoff¹⁶ the blood picture was not altered. In another case of cyclic agranulocytosis reported by Fullerton and Duguid⁴ splenectomy was beneficial. In the case of Fullerton and Duguid the spleen was found to be 3 to 4 times normal size and rheumatoid arthritis had existed for 17 years, so that the question of classification is raised. The case may well be an example of Felty's syndrome. In the case of cyclic agranulocytosis recorded by Owren¹³ the removal of an enlarged spleen was not beneficial. Weiss and Collins²² have reported a case of chronic neutropenia in which a favorable hematologic response followed removal of a spleen that weighed 250 gm. Their patient was a male, aged 19 years, without joint manifestations, but with diabetes.

The difficulties of classification of a case of neutropenia existing with or without splenomegaly, arthritis or hyperplastic bone marrow and depending upon results of splenectomy as demonstrated are great. In some instances the descriptive term of hypersplenism is certainly more appropriate. Peden²⁴ has reported 2 cases with neutropenia, splenomegaly, atrophic arthritis, anemia, elevated basal metabolic rates and chronic nonhealing ulcers. This author stated that these cases did not permit classification among well recognized syndromes and considered them as examples of hypersplenism.

As demonstrated in the fifth case reported herein not all cases with chronic neutropenia are benefited by splenectomy. This has been emphasized recently by Spaet and Dameshek. The presence of splenomegaly and the degree of enlargement constitute a most important and helpful aid to the clinician in the preoperative determination of which case of neutropenia will be benefited by splenectomy. The greatest benefit from splenectomy in cases of neutropenia

due to hypersplenism occurs in those cases with well marked splenic enlargement that can be determined clinically. The case reported by Hattersley⁶ is illustrative. In this case severe chronic neutropenia without splenomegaly was observed. The bone marrow was cellular. No improvement was obtained by the removal of a spleen which weighed 150 Gm. Hattersley concluded that the lack of splenomegaly should be considered a contraindication for splenectomy. In case 1 of this report, the patient did not have a large spleen. While splenectomy benefited some of the clinical manifestations of hypersplenism, the results were not comparable to the case of primary splenic neutropenia reported by Rogers and Hall¹⁷, in which removal of a large spleen was curative. Splenectomy appears worth while in cases of neutropenia with splenomegaly and should be considered in all such instances. It may be of some benefit in cases without demonstrable splenomegaly, but data on these cases should be analyzed in greater detail before splenectomy is advised in view of the possibility of the failure of a cure.

SUMMARY

Five cases in which chronic neutropenia was treated by splenectomy are reported. In 4 of the cases there was clinical evidence of hypersplenism and these cases received variable degrees of benefit. The fifth case was one of chronic hypoplastic neutropenia.

Diagnostic difficulties are encountered in the differentiation of primary splenic neutropenia, Felty's syndrome, splenic panhematopenia, cyclic periodic neutropenia and chronic hypoplastic neutropenia because of the overlapping in the clinical characteristics of the syndromes.

The type of case with neutropenia most benefited by splenectomy is one with clinically demonstrable splenic enlargement and a hyperplastic bone marrow.

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LATE COMPLICATIONS FOLLOWING THE REMOVAL OF THE RUPTURED SPLEEN

REPORT OF TWO CASES

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After a surgeon has operated upon a patient for a rupture of the spleen and has done a splenectomy, he is invariably asked many questions. How can the patient live without his spleen? How will it affect him? Will he be able to lead a normal life? The answer is that the patient should be able to lead a normal life without any ill effects referable to splenectomy.

The spleen has for many years been the object of much investigation and considerable research. The function of the spleen is not completely understood. Most splenectomy patients do well and have little difficulty following the initial phase of their surgery. Complications are few, but, we should realize that complications do arise and we should be on the lookout for them. With this in mind, I wish to review some of the literature and report 2 cases showing late complications of splenectomy for traumatic rupture.

In the foreign literature, de Francis and Guidetti⁵ reported a series of 19 cases. They surveyed these cases late after surgery and they thought their patients showed less muscular energy and tendency to easy fatigue. Many of their patients had to change occupations, seeking ones less burdensome. They also thought their patients had less resistance to infections following splenectomy and many of them displayed an increase in appetite. Other foreign writers³ re-examined 18 patients following splenectomy for traumatic rupture. The average time elapsed after operation was 12 years. They came to the conclusion—after extensive study including bone marrow studies and various blood studies—that clinical changes after splenectomy were slight. Several of their patients complained of being unable to do things that required any great physical exertion. They reported no serious complications.

Foster and associates⁴ reviewed a series of 20 cases and found that the two most common complications were wound disruption and intestinal obstruction. In their cases of obstruction, the complications occurred in the early postoperative days. Wilson¹⁴ reported 1 case of a patient who developed intestinal obstruction on the ninth postoperative day. Rahme¹¹ described a 29 year old patient who was operated upon for bowel obstruction six years after a splenectomy for traumatic rupture of the spleen. At operation, a cord-like adhesion was found with angulation of the small bowel. Hyperplastic hemolymph nodes were also found forming a tumor in the mid-jejunum. The tumor proved to be hyperplastic hemolymph nodes having taken on the characteristics of splenic tissue except for the trabeculae. Another case of nodular splenic implants was reported by

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Hamrick and Bush.⁷ Their patient was a 9 year old boy who had a splenectomy for traumatic rupture. Thirty-nine months later he died of tetanus. An autopsy was done and nodular splenic implants were found throughout the peritoneal cavity.

Wise¹⁵ reported a case of a 24 year old white man who was operated upon for traumatic rupture of the spleen. Three months after operation, he was reoperated upon for intestinal obstruction. A band from the ileum to the mesentery was found and divided. Eight months later, he had severe pain and again presented a picture of intestinal obstruction. He was operated upon again and a band similar to the first was removed. At the last operation, numerous splenic implants in the omentum and part of the omentum were removed.

Krueger and Mast⁸ recorded a case of a patient who was operated upon first at the age of 11 years. Five years later, the patient complained of pain and cramping in the left upper quadrant and was explored again. Twenty to 30 brownish-red, soft, encapsulated nodules, ranging from 1 to 2 cm. in diameter, were found attached to the omentum. The nodules resembled spleen and pathologically were diagnosed as inflammatory, small accessory spleens. Numerous adhesions were found in the left upper quadrant. These authors reviewed the literature and collected a few other cases of patients with splenic implants which were found on the abdominal viscera following the removal of a ruptured spleen. They were under the impression that the determining factor causing this condition was trauma and not splenectomy, since it is true that these splenic implants are usually not found following splenectomy for conditions other than trauma.

Storsteen and ReMine¹² recently reviewed the literature and reported splenic implants following splenectomy for trauma. They added 1 case of a 22 year old man treated by splenectomy for a ruptured spleen in 1946, and in 1951 he was reoperated upon by the writers for intestinal obstruction. At operation, they found the small intestine adherent to the anterior abdominal wall beneath the old scar. Between 300 and 400 splenic nodules were found along the small intestine, colon, omentum, mesentery and parietal peritoneum. They thought that splenic implants usually cause no trouble, but advised that surgical technic of elective splenectomy should be done as carefully as possible to prevent accidental rupture.

Byrne¹⁰ reported a series of 101 cases of splenectomy for trauma. The mortality rate was 16.8 per cent and the presence of multiple injuries was the immediate cause of death in the majority of patients, especially in those patients with gunshot wounds of the abdomen. He reported no late complications. Martin and Cooper and others⁹ reviewed the literature on 777 splenectomies done for all conditions of the spleen and they reported thrombosis, hemorrhage and infections as the major complications. It has been shown that thrombosis of the portal and splenic veins may also be a complication following removal of the ruptured spleen.⁶ Prolonged fever, abdominal pain—sometimes related to food intake—abdominal distension, increased leukocyte count, increased platelets and erythrocyte sedimentation rate—following splenectomy—should suggest to the surgeon the possibility of this complication.

The following cases are reported to show late complications following splenectomy for trauma.

CASE REPORTS

Case 1. J. D., a 9 year old white boy was first seen in the Emergency room of St. Joseph Hospital on Feb. 5, 1950 with a history of running into a post approximately one hour previously. At the time of examination he complained of epigastric pain which was not severe. He had no elevation of temperature; no abdominal distension; no tenderness except over the epigastrium which appeared to be in the muscles. He was next seen in the afternoon of the following day, at which time his temperature was 102 F. and he revealed some abdominal distension and tenderness in the left side over the costal margin. He was unable to lie down and his respirations were somewhat rapid. A diagnosis of ruptured spleen was made and an emergency splenectomy was done at that time. His convalescence was good and he was discharged from the hospital on February 13. He later was seen on Aug. 8, 1950 and placed in the hospital for one day for observation for suspected appendicitis. His general health was good until the first part of May 1952. At that time he again was seen because of a complaint of pain in the upper abdomen with nausea and vomiting which started two days previously and had become more severe. Roentgenograms of the abdomen were taken at that time and showed a complete intestinal obstruction. He was operated upon soon after admission to the hospital. Upon opening the abdomen a large adhesive band was found running from the upper part of the ileum to the root of the mesentery. This produced a complete angulation of the bowel with obstruction. There was no evidence of splenic implants. The obstruction was released and the patient subsequently was returned to his room in good condition. His convalescence was uneventful and he was dismissed May 11, 1952. Since then, the patient has done very well and has had no recurrent attacks of obstruction.

Case 2. R. M., an 18 year old white man had been in an automobile accident in February 1952 at which time a splenectomy was done for a ruptured spleen. His convalescence was good and he had no trouble until the present episode. He was first seen on May 2 with complaints of colic-like pains in the abdomen with nausea and vomiting. This condition started about 20 hours prior to his admission to the hospital and became progressively more severe. The pain was more generalized in the upper abdomen. This patient, when first seen, was doubled over holding his stomach. On examination there was generalized tenderness throughout the entire abdomen. The tenderness was more severe in the left upper abdominal region. A roentgenogram of the abdomen was taken which showed ascites and dilated loops of small bowel. He was observed for 5 to 6 hours and became worse. A clinical diagnosis of intestinal obstruction in the upper small bowel was made. At operation a large adhesive band was found at the junction of the upper and middle thirds of the ileum which extended to the root of the mesentery. No splenic implants were found. The large band was divided and the obstruction released. The patient was returned to his room in good condition. Following operation he vomited some blood. This vomiting soon subsided and the post-operative convalescence was excellent. He was dismissed from the hospital on May 6, 1952. His general condition since then has been very good.

DISCUSSION

Late complications following splenectomy for trauma are fairly rare. According to the literature, the main complications are the production of large adhesive bands in the upper abdomen which produce small bowel obstruction; splenic tissue implants in the omentum and on the abdominal viscera. These implants have been reported to produce obstruction. These two main conditions have been reported as occurring at the same time or separately. It is believed by some writers that the splenic implants are secondary to trauma to the spleen and not secondary to splenectomy.

SUMMARY

The literature has been reviewed and late complications of splenectomy for trauma have been discussed.

Two cases of patients having large adhesive bands as the cause of small bowel obstruction in the upper ileum following splenectomy for trauma have been reported. The first patient developed obstruction approximately two years following splenectomy while the other patient developed obstruction three months following splenectomy.

A discussion of the late complications following splenectomy for trauma has been presented.

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TREATMENT OF CARCINOMA OF THE BREAST: THE SUPER-RADICAL OPERATION

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The development of surgery of the breast reflects the advance in the surgical management of all cancers. In 1867, Charles Moore²⁹ advised the excision of the entire breast in patients with breast cancer. Samuel W. Gross¹³ in 1880 recommended dissection of the axilla when the axillary lymph nodes were involved with metastatic cancer. In 1889, Lothar Heidenhain²⁵ of Berlin removed the superficial part of the *pectoralis major* muscle and the entire *pectoralis major* muscle when the carcinoma was adherent to the chest wall. William S. Halsted²⁰ in 1894 standardized the operation of radical mastectomy for carcinoma of the breast. In the same year (1894) Willy Meyer²⁸ reported a similar operation.

Since Halsted's communication in 1894 there have been few changes in his operative technic of radical mastectomy. He taught that to attempt to close the breast wound more or less regularly by any plastic method was hazardous, and should be vigorously discountenanced. Many surgeons are ardent followers of the Halsted principle of radical mastectomy while on the other hand there are equally ardent followers of Sampson Handly who advocated extensive removal of fascia with primary skin closure.²² Brooks and Daniel⁶ have expressed the opinion that "There is no such thing as a radical operation for carcinoma of the breast as there is a Billroth II for carcinoma of the stomach." For many patients with cancer of the breast the standard operation of radical mastectomy is not extensive enough to remove all the involved lymph nodes. Those patients with metastatic carcinoma in the supraclavicular or internal mammary lymph nodes can not be cured by the Halsted operation. Dr. Halsted wrote, "Dr. W. H. Cushing, my house surgeon, has in three instances cleared out the anterior mediastinum on one side for recurrent cancer. It is likely, I think, that we shall in the near future remove the mediastinal contents at some of our primary operations."²¹ He did not follow up this idea, however. Gordon-Taylor¹⁴ (1948) removed the anterior mediastinal lymph glands with the internal mammary vessels after resection of the second and third costal cartilages in carcinoma of the breast. Wangenstein (1950) extended the radical operation to include a radical neck, supraclavicular, and mediastinal dissection.^{45, 46} Ehrenhaft¹¹ (1951) reported *pneumonectomy with extensive hilar lymph node resection* for metastatic breast carcinoma in the lung. Gardner,¹² (1951) at Duke University, has combined supraclavicular and internal mammary chain dissection with radical mastectomy. Urban⁴⁴ (1952) has resected the chest wall from the first to the fifth interspace including the costal cartilages, a 1 centimeter wide segment of the sternum, the internal mammary lymph nodes and blood vessels, and the underlying pleura. This segment of chest wall is removed in continuity with the pectoralis muscles.

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Any operation for carcinoma of the breast is incomplete which does not remove all the potential lymphatic drainage, a *sine qua non* in cancer surgery. No doubt there are patients with axillary metastases from breast cancer who have had beautiful operations only to have the supraclavicular lymph nodes become involved by metastatic cancer two to three years later. In such a patient, a cure could probably have been obtained if those nodes had been removed at the time of or shortly after the primary operation. A careful selection must be made of those patients who might be benefited by the extended operation as done by Dr. Wangenstein. Any statistical justification for the extended operation must of necessity await the study of many years. From a theoretical point of view, however, the extended operation has merit because more lymph tissue which drains the breast can be removed.

From Stibbe's⁴¹ anatomic studies the importance of the parasternal lymph node chain is readily appreciated in carcinoma of the breast. This has been borne out by the recent biopsy studies by Scott and Conerly³⁷ at Vanderbilt University Hospital of the internal mammary nodes of the second interspace of women with breast cancer. Dahl-Iverson and Soerensen¹⁰ in a study of 43 patients with primary operable breast cancer found 10 to have metastases to the internal mammary lymph nodes at the time of radical mastectomy. R. S. Handley, reported by Urban,⁴⁴ in a review of 100 primary operable breast cancers, found by biopsy during the radical operation that there were metastases to the internal mammary lymph nodes in 60 per cent of those lesions located in the medial half of the breast and in 20 per cent of those located in the outer half of the breast. In a study of the internal mammary chain of lymph nodes in 39 autopsies Boerge Soerensen⁴⁰ (1951) of Copenhagen found an average of 3.5 nodes per interspace for each patient. In only 1 patient was there a lymph node in the fifth interspace. The greatest number was found in the second interspace with decreasing frequency for the third, first and fourth interspaces, in that order. Not until recently have surgeons made an attempt to salvage with surgery patients who have metastatic involvement of the parasternal nodes. This has been made possible because of a better understanding of the anatomic and physiologic factors involved in an operation of this magnitude. With blood and blood derivatives, antibiotics, and better anesthesia, the super-radical operation for cancer of the breast can be done without a prohibitive mortality rate in those patients without advanced cardiovascular disease.

BETTER SURGICAL RESULTS IN THE LYMPH NODE NEGATIVE GROUP

The five-year survival rate for patients treated by surgical intervention for carcinoma of the breast depends upon the stage of the disease. Stage I represents patients with cancer localized to the breast, without involvement of the skin or lymph nodes, or attachment to deeper structures. Stage II includes similar patients but with some axillary lymph node involvement. Stage III includes patients with skin involvement, satellite tumors, fixed tumors, and extensive axillary lymph node metastases. Stage IV consists of patients with evidence of distant metastases.³⁸ By stage of the disease I refer to the anatomic extent of the

disease at the time of treatment and not to the time factor. The time factor is important, however, because with the increase of time the disease will advance from one stage to another. The delay period from onset of the disease to the time of treatment is the time factor of importance. Even a long delay period may not alter the stage of the disease or the prognosis for survival. On the other hand, a short delay period does not preclude the absence of metastases. All other things being equal, however, the longer a tumor is present, the greater the opportunity for growth and spread of the neoplasm. Other factors such as the biologic properties of the neoplasm and possible host resistance may also influence the stage of the disease.

All stage I carcinomas of the breast should be cured by simple mastectomy. Because death does occur from carcinoma of the breast in the apparent stage I disease, it is a measure of the clinical and pathologic limitations in the detection of metastases. In table I the differences in five-year survival rates with and with-

TABLE I
Some results of radical operation for carcinoma of the breast

Author	Yr.	Group I Without Axillary Metastasis			Group II With Axillary Metastasis		
		Number of Patients	Five-Year Survivals Per Cent	Ten-Year Survivals Per Cent	Number of Patients	Five-Year Survivals Per Cent	Ten-Year Survivals Per Cent
Adair ²	49	737	78.6		1173	42.4	
Brooks and Daniel ⁸	40	12	91.6		60	26.7	
Gordon-Taylor ¹⁴	48	113		84.0	204		29.4
Haagensen and Stout ¹⁶	42	237	61.2		385	21.0	
Harrington ²⁴	46	2427	75.7	57.9	3728	30.4	16.4
Orr ²²	49	77	64.9	24.6	89	26.9	8.9
Simmons ³⁹	42	42	73.0	70.0	99	30.0	18.0

out axillary metastases can be readily appreciated. The failure to diagnose metastatic disease may be due to the following: (1) nondemonstrable lesions by unusual routes to distant areas; (2) failure to examine all regional lymph nodes; (3) failure to expose metastatic cancer cells by the routine methods of cutting two to three sections from the larger lymph nodes in the pathology laboratories. The observations of Saphir and Amromin²⁶ are interesting and significant. In 30 patients with breast cancer in whom the axillary lymph nodes were reported negative by the usual routine methods they found 10 patients (33.3 per cent) to have metastatic cancer when the serial section technic of study was applied. From the above observations, therefore, the following are noteworthy: (1) the potential lymphatic drainage of the breast is extensive; (2) the regional lymph nodes are involved in a larger proportion of patients than current routine laboratory studies indicate.

In contradistinction to the usual surgical management of carcinoma of the breast is that advocated by McWhirter²⁷ who reported that a combination of simple mastectomy and immediate postoperative radiation yielded better sur-

vivals after five years than radical mastectomy. The five-year survival of all patients was 43.7 per cent. With McWhirter's technic the mastectomy is as limited as possible, whereas a minimal tumor dose of 3,750 roentgens is given through four fields within a period of three weeks. This dose of radiation is higher than that usually used in the United States, but is made possible because there is a minimum of fibrosis and avascularity to interfere with the effects of radiation.

Keynes²⁶ (1937), unlike McWhirter, used long needles containing 3 mg. of radium element placed about the tumor, in the axilla and above the clavicle. They were usually left in place for seven days. His plan of management had serious drawbacks, including the failure to cure cancer.

With surgery we plan to separate the patient from her disease. It is therefore, an extirpative maneuver, whereas irradiation is a suppressive agent which slows down the rate of growth of cancer. Most investigators believe that irradiation is generally ineffective in sterilization of metastases in lymph nodes.¹⁸ Wood and Boag⁴⁸ on the other hand, believe that metastatic carcinoma in lymph nodes is *radiocurable*. That irradiation therapy is of value in the treatment of advanced breast cancer to relieve pain and prolong life, has been accepted by almost everyone interested in the subject. This can not be said for preoperative and postoperative irradiation. Many surgeons have advocated preoperative irradiation as a useful procedure in treatment of cancer of the breast.^{35, 5, 33} Berven⁴ (Univ. of Stockholm) recommended preoperative irradiation in all patients with stage I and II disease. Preoperative roentgenotherapy has been abandoned, however, by most clinics in America.^{23, 1} Bainbridge³ reported 11.53 per cent five-year survival rate in those patients receiving preoperative irradiation in contrast to a 33 per cent survival of 5 to 36 years for those patients who had radical surgery alone. Most investigators advise postoperative irradiation in those patients with stage II and III disease. Taylor⁴² does not believe preoperative or postoperative irradiation increases the number of cures or defers recurrences. Shimkin³⁸ found no statistically significant improvement in those patients who received postoperative irradiation at the University of California Hospital. Byrd⁸ in his communication on postoperative irradiation therapy in patients with breast cancer at Vanderbilt University Hospital, found no statistically significant improvement in the five-year survival rate. Of 39 patients with carcinoma of the breast and axillary metastases treated with radical surgery and irradiation only 8 (20.5 per cent) were alive and clinically well at the end of five years. Of 97 similar patients treated with surgery alone 21 (21.6 per cent) were clinically well after five years. Parker and Lees,³³ in their study of the true curability of cancer of the breast, make the following statement. "It has not been proved that the survival rate of cancer of the breast, using the five-year survival rate as an index, is affected by treatment at all," and "The evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread."

From the above statistical studies of the results of treatment of breast cancer in stages II and III disease it would seem that the extended operation has a place in the surgical therapy of selected patients.

Each patient with cancer of the breast must be considered as an individual to whom the accumulated statistics may not apply. Each patient has but one life to live and that life is dear to her. Therefore, the surgeon should weigh carefully all the presenting factors in determining the course of treatment. Where there is a chance for cure by surgical intervention, even though it may be a small one, the patient is entitled to that chance. Obviously, radical surgery is not indicated in those patients with widespread cancer. A few patients in stage III disease will be salvaged by radical surgery. The absolute physical contraindications to radical surgery for breast cancer as outlined by Haagensen and Stout¹⁷ are as follows:

1. When the carcinoma is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When satellite nodules are present in the skin over the breast.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular nodes are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two or more of the following signs of locally advanced carcinoma are present: (a) ulceration of the skin; (b) edema of the skin of limited extent (less than one-third of the skin over the breast involved); (c) fixation of the tumor to the chest wall; (d) axillary lymph nodes measuring 2.5 cm. or more in transverse diameter and proved to contain metastases by biopsy; (e) fixation of axillary lymph nodes to the skin or to the deep structures of the axilla, and proved to contain metastases by biopsy.

Brooks and Proffitt⁷ reported 6 patients with breast cancer discovered during the periods of lactation or pregnancy at Vanderbilt University Hospital between 1925 and 1948. All of these patients except 1 were dead within two years from the time they were first observed. The patient who was the exception lived for 15½ years. She received both preoperative and postoperative irradiation. Geschickter¹³ (1945) could find no report of a cure for carcinoma of the breast operated upon during pregnancy. Tomlinson and Eckert⁴³ (1949) applied the criteria of inoperability established by Haagensen and Stout to all cases of breast carcinoma seen at Barnard Free Skin and Cancer Hospital between 1933 and 1943. There were 167 patients who fell into the categorically inoperable group. In 100, routine radical mastectomy or some similar operation was done, and in the other 67, only roentgenotherapy was used. Of the surgical patients 2 were well and clinically free from carcinoma at the end of five years, 1 for 8 years and the other for 14 years. Both had carcinoma associated with pregnancy or lactation. Wells⁴⁷ (1950) reported 5 patients with carcinoma of the breast diagnosed during pregnancy or lactation at Hartford Hospital between 1932 and 1938. Two were treated with irradiation and both died, 1 after 8 months and the other after 17 months. Three patients were treated with radical mastectomy. Two of these were living and clinically well 12 years after operation. The third patient died 13 months after operation. Because there are reported apparent cures of carcinoma of the breast developing during pregnancy or lactation Haagensen and Stout

(1951) make the following statement: "The existence of such cases, few though they may be, invalidate the first provision in our rule for judging operability, the provision in which we classed these patients as inoperable."¹⁹ They report no cure of carcinoma for the breast developing in patients during lactation or pregnancy.

The five-year survival rate is very low for those patients with inflammatory carcinoma of the breast. Chris⁹ (1950) found 220 cases of inflammatory carcinoma in the literature with 5 recorded as surviving five years or more.

INDICATIONS FOR THE SUPER-RADICAL OPERATION

At the University of Minnesota Hospital the super-radical operation for carcinoma of the breast is used in those patients with axillary metastases diagnosed clinically or at operation. It is used, therefore, most often in stage II and occasionally in stage III of the disease. In those patients with previous radical operations for breast cancer, the appearance of enlarged supraclavicular lymph nodes is considered an indication for the extended procedure. Those patients with primary cancer in the medial quadrants of the breast are also considered candidates for the operation. Those patients with ulceration of the skin over the lesion and with fixation of the tumor to the chest—classified by Haagensen and Stout as inoperable—might be well considered for the super-radical operation. Of 18 such patients reported by Koefoot and quoted by Wangenstein, 4 (22.2 per cent) were alive and well five years after radical mastectomy.⁴⁶ It may be well to consider the extended procedure for patients with breast cancer developed during pregnancy or lactation and for those with inflammatory carcinoma of limited extent.⁴⁵

TECHNIC OF THE PROCEDURE

In short the operation includes the following: "1. The conventional radical mastectomy and axillary dissection. 2. A supraclavicular-cervical dissection extending as high as the upper border of the thyroid cartilage. 3. Excision of the entire parasternal lymph node chain, including the internal mammary blood vessels from the site of origin of the internal mammary artery from the subclavian artery and the termination of the internal mammary vein into the subclavian vein, to the fifth interspace below. 4. A mediastinal dissection with partial or complete thymectomy, together with removal of the lymph node bearing tissue along the homolateral innominate vein, and the contralateral innominate vein as well, if lymph node enlargement is present. On the right side, the lymph node bearing tissue is removed along the entire length of the superior vena cava; on the left side the dissection parallels the carotid and subclavian arteries and stops when the left pulmonary artery is uncovered."⁴⁶

The skin incision extends from the lateral mid-neck region collar fashion anteriorly and downward across the suprasternal notch and the sternum to the level of the fourth interspace. The sternum is vertically divided to the same level and the sternal knife is directed into the fourth interspace toward the diseased side. The smaller sternal fragment is transected at the level of the first interspace. For adequate mobilization of the clavicle for better dissection of the supraclavicular

neuro-vascular bundle the greater part of the first rib must be resected. Too, the resection of the first rib prevents angulation and compression of the subclavian vein, and therefore, removes one of the factors responsible for postoperative edema of the upper extremity.

Care must be exercised to avoid injury to the vagus, recurrent laryngeal, and phrenic nerves. If the thoracic duct is severed it must be ligated. Parts of the pleura should be removed if involved in the disease. The mediastinum is drained by two no. 24 F. catheters with continuous suction or by a dual-tube with an air break if the pleura has not been opened.³¹ To minimize the postoperative morbidity firm fixation of the sternum must be obtained.³⁰ The operation should be done in two stages. First the standard radical operation should be done followed by the extended operation after six to eight weeks. Unless contraindicated, the remaining breast should be removed by simple mastectomy as advocated by Brooks⁷ and Wangenstein.⁴⁶

RESULTS

Wangenstein⁴⁶ has done 47 super-radical operations. Of these, 44 were for carcinoma of the breast; one for fibrosarcoma of the breast with parasternal and axillary lymph node metastases; one for a malignant melanoma of the skin over the trapezius muscle; and one for lymphosarcoma of the parotid gland with cervical lymph node metastases. There were six hospital deaths (12.7 per cent). Five of the deaths occurred in 28 patients in whom the super-radical operation was done as the primary procedure. One death occurred in 16 patients who had had previous radical mastectomy. The average age of the patients who died was 63 years. Three of the 6 patients died with convulsions 48 hours following operation. These deaths were thought to be due to cerebral air embolism. Two deaths were from hemorrhage which developed late in the convalescent periods. One of these followed a wound infection and puncture of the subclavian artery by a small spicule of bone from the sternum. The other developed a spontaneous hemorrhage from a minute hole in the common carotid artery, the site of an undetected vas vas. The sixth death was in a 59 year old woman who proved to have active pulmonary tuberculosis with large tuberculous and large cancerous mediastinal lymph nodes.

CASE REPORT

Miss V. E., aged 29, was admitted to Mid-State Baptist Hospital one year after noting a small mass in the upper outer quadrant of the left breast. Biopsy revealed carcinoma. A radical mastectomy with primary skin grafting was done. Cancer was noted in five axillary lymph nodes at operation. The wound was healed in three weeks. Seven weeks after the Halsted radical mastectomy, the extended procedure of Wangenstein was done at Vanderbilt University Hospital. No metastatic cancer was noted. The patient received six pints of blood during the procedure. The left phrenic nerve was inadvertently severed at the point of passage beneath the clavicle. She withstood the procedure without a fall in blood pressure or the development of a cardiac arrhythmia. Seven hundred cc. of sero-sanguinous fluid were removed from the chest during the first 36 hours after operation, 300 cc. during the next 24 hours, and only 50 cc. thereafter until the dual tubes were removed. Four hundred cc. of air were removed from the left chest 18 hours after operation and none thereafter.

Morphine was administered only during the first two postoperative days. She recovered rapidly and was discharged on the morning of the ninth postoperative day. Sixteen months later she developed pain in the right hip region. There was no apparent evidence of recurrence in the chest or lungs, however, there was roentgenographic evidence of metastatic tumor in the right ischium and inferior ramus of the right pubic bone. This area of metastasis was treated with deep roentgen ray therapy using 4,000 roentgen units through three portals and a castration dose of roentgen ray was given over both ovaries. Menstruation stopped and all pain ceased.

This patient was one of two daughters. The sister developed cancer of the left breast at the age of 27 and lived only three years following radical mastectomy.

SUMMARY

Whether the super-radical operation for carcinoma of the breast will ultimately increase the true survival rate remains to be seen. The mortality rate from the procedure will be greater than that following the more conventional radical operations. It can be said for the operation that it represents the most extended surgical procedure yet devised for removal of the potential lymph drainage of the breast.

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THE EFFECT OF ACUTE PARTIAL AND COMPLETE OBSTRUCTION OF THE THORACIC AORTA IN THE DOG*

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INTRODUCTION

The cardiovascular effect of partial or complete obstruction of the aorta is of interest in the surgery of thoracic aneurisms and coarctation of the aorta. An appreciable amount of work has been done to study the effects of occlusion of the aorta, but always in the open chest of the dog. With the possibility that the open chest might interfere with the normal physiology we have attempted to study the subject in anesthetized dogs with the chest closed.

METHODS OF INVESTIGATION

A logical method for the production of experimental acute coarctation of the thoracic aorta in the closed chest would be a method of external compression. A clamp was devised that could be manipulated externally with which a varying degree of aortic obstruction could be produced in a few seconds.

A polyethylene tube, size no. 410, was sectioned so that $\frac{1}{4}$ of the circumference of the tube was left projecting to form a loop. This was connected with a steel wire inside of the polyethylene tube to which, in turn, was attached by a swivel to a copper screw mechanism set into the opposite end of the tube (fig. 1A). The flattened loop was placed around the aorta. This loop could be drawn into the polyethylene tube and tightened about the aorta by rotation of the screw.

The dogs used in the experiments varied in weight from 7.6 to 11.0 Kg.

The first stage of the experiments consisted of the placement of the loop around the aorta. In order to do this, the dogs were anesthetized with ether and oxygen. The chest was entered by resection of the fifth or sixth rib (fig. 1B), and the loop was placed around the aorta, a distance of 2 to 3 cm. distal to the subclavian artery, in such a way that no obstruction was produced. The free end of the tube with the screw was extended through the fourth or fifth intercostal space posteriorly and placed subcutaneously. The sympathetic chain invariably had to be transected at this interspace. The length of the tube and the size of the loop was determined at this time, varying in accordance with the thickness of the chest wall and the diameter of the aorta.

The second stage of the experiments, 12 to 36 days after the first stage, consisted of studying the effects on the cardiovascular system, during the production of the acute partial and complete obstructions of the aorta. The dogs were anesthetized with 8 mg. of morphine sulphate per Kg. of body weight given subcutaneously and an average of 15 to 20 mg. of nembutal per Kg. of body weight

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given intravenously. The screw was easily exposed through the skin and could be manipulated without difficulty (fig. 2).

The diameter of the aorta was measured when the loop was placed at the first operation, and after completion of the experiments the dog's chest was again entered and the degree of obstruction measured. An estimate of the degree of obstruction was calculated by the number of turns of the screw.

Ballistocardiograms were taken in 10 dogs using the torsion ballistocardiograph devised by Reissmann.¹⁶ Five of the 10 dogs had ballistocardiograms taken before operation. In 4 of them the cardiac output was measured in the following manner:

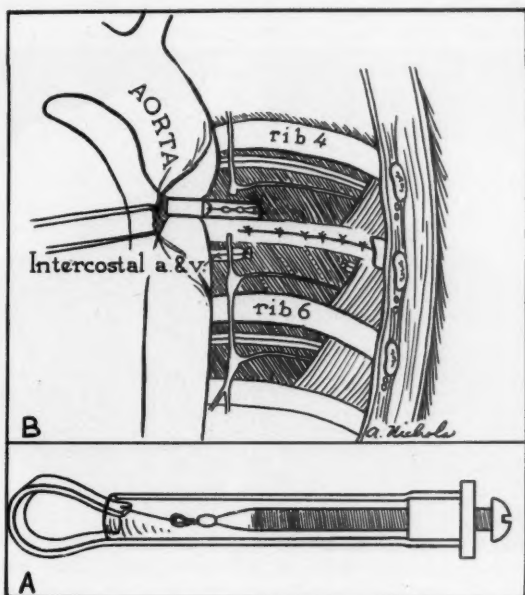


FIG. 1. (A) Illustration of the clamp and (B) placement of the loop around the aorta. For description see text.

1. By placing a Cournand needle, size 18, in the femoral artery through which samples of blood for oxygen saturation were removed.

2. Through the right external jugular vein the pulmonary artery was entered via the heart,⁶ using a radiopaque cardiac catheter, placed by fluoroscopy. The oxygen content of the mixed venous blood was withdrawn through the tube and measured.

3. Through an intratracheal tube, the oxygen consumption was measured from the tracings of the modified spirometer of the Benedict-Roth type.

4. Cardiac output was calculated by the direct Fick method, utilizing the manometer apparatus of Van Slyke and Neill,¹⁹ for determinations of oxygen content in the blood samples.

Pressure recordings were made with Cournand needles in the femoral and right carotid arteries. Between arterial recordings of blood pressures and sampling, a stylet dipped in a solution of heparin was placed in the lumen of the needles to prevent clotting. Arterial pressures were measured with the Sanborn electromanometer and recorded on the Sanborn polyviso simultaneously with electrocardiogram and ballistocardiogram.

The experiments extended over a period of two to three hours.

RESULTS

In 4 of the 10 dogs, determinations of the pressures in the carotid and femoral arteries were studied in conjunction with the cardiac output and the ballistocar-



FIG. 2. Dog lying on right side. Visible are the incision and extremity of the polyethylene tube with the screw.

diagrams,* by methods previously described. The results were similar in the 4 dogs. Representative data are reproduced in table I.

During the progressive occlusion of the thoracic aorta we noticed increasing changes as follows:

Above the stenosis: The first effect of clamping on the blood pressure was on the systolic aortic pressure which started to increase with 60 per cent obstruction of the aortic lumen. The diastolic pressure showed a definite increase with further obstruction (80 per cent). The maximum changes in the systolic and diastolic pressures were with 95 per cent obstructions.

Above the obstruction the pulse pressure wave showed a progressively less

* Sincere appreciation is extended to Dr. Kurt R. Reissmann for his cooperation in interpreting the tracings of the blood pressures, and ballistocardiograms; also, to the team which made the acute experiments possible.

steepening, and the peak of the pressure wave occurred later. Vibrations appeared on the ascending limb of the tracing and on the crest of the wave (fig. 3C (a, b)). As the hypertension increased the vibrations became progressively more pronounced. A slight decrease in pulse pressure was noted.

Below the obstruction, the systolic pressure decreased at a more rapid rate than the diastolic pressure. With 60 per cent obstruction there was a marked drop in the systolic femoral pressure while the drop in the diastolic pressure appeared only with 80 per cent obstruction of the lumen. A progressive broadening and rounding of the crest of the pulse wave, in the femoral artery was noted with a gradual increase in pulse pressure, until it appeared as a smooth line. Above the stenosis the average systolic increase was 20 mm. of Hg and the diastolic 8 mm. In contrast, the average femoral systolic drop was 62 mm. and the diastolic drop was 43 mm. of Hg. In 2 dogs the femoral pulses were imperceptible.

These results are in agreement with the work of Katz,¹² Dow,⁷ and Gupta and Wiggers.¹⁰ Wiggers produced different degrees of coarctation in dogs with the

TABLE I

Per cent obst.	Pulse rate	Blood pressure in		Cardiac output	Stroke volume	O ₂ Cons. L./m.	O ₂ content in		Respiratory rate
		carotid	femoral				femoral	pulmonary	
0	190	150/110	165/110	1.52	8.0	7.0	16.2	11.6	8
60	187	160/110	145/110	1.63	9.0	7.0	16.4	12.1	12
80	180	155/120	108/100	1.58	10.0	7.6	15.0	10.2	13
95	155	173/138	20/20	1.12	7.2	5.6	13.7	8.8	15

Per cent obstruction refers to cross section at the site of stenosis. Blood pressures in mm. of Hg. Cardiac output in liters per minute. Stroke volume in cc. Respiratory oxygen consumption in liters per minute. Oxygen content in the femoral and pulmonary artery in volume per cent.

chest open, using a special calibrated compressor devised by Finneberg and Wiggers.⁸ They concluded that a reduction of more than 45 to 55 per cent in the aortic lumen was required before arterial pressure changes were produced in the aorta and in the femoral artery. Increasing obstruction (55 to 65 per cent) caused the average systolic pressure to increase. Above 65 per cent, the systolic femoral pressure decreased to a greater extent and the diastolic aortic pressure increased slightly. The maximum aortic increase in the systolic and diastolic pressures occurred with almost complete obstruction (90 per cent). In respect to the femoral pressures, the decrease in systolic pressure was greatly accelerated beyond 55 to 65 per cent, the diastolic following the systolic in a lesser degree. At approximately 85 to 95 per cent obstruction the femoral pulse was just discernible.

The effect of the obstruction on the heart rate in our dogs was a bradycardia, the degree of which increased with further obstruction of the lumen.

The average cardiac output increased in all dogs but 1. The stroke volume increased in all. Minimum changes in the respiratory oxygen consumption rate per minute and the progressive decrease in saturation of the mixed venous blood

from the pulmonary artery and femoral arterial blood, taken just below Poupart's ligament were noted (table I).

DISCUSSION

The effect of various degrees of obstruction of the aorta on the blood pressure above and below the obstruction can be explained on a mechanical basis. Numer-

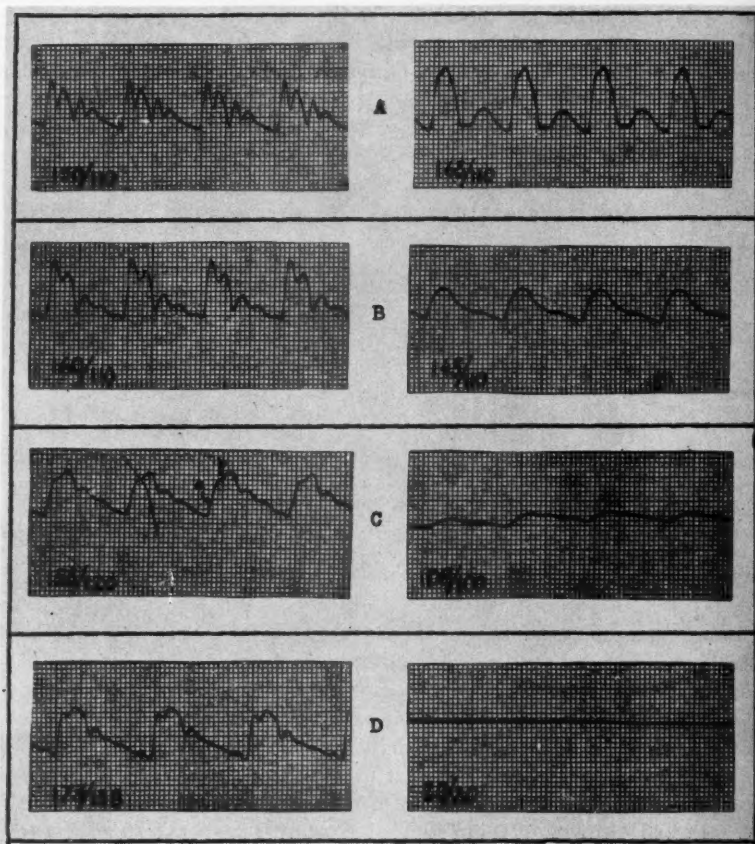


FIG. 3. Effects of progressive obstruction of the thoracic aorta on the contour of the carotid (left) and femoral (right) pressure curves. Segment A, control with no obstruction; segments B, C, and D show the effects of 60, 80 and 95 per cent reduction in the aortic lumen at the site of obstruction.

ous authors have demonstrated the effects of clamping the aorta in the open chest on the heart alone and in the presence of shunts.^{1, 2, 5, 11, 9} In our experiments, obstruction of 50 per cent of the aortic lumen was tolerated without any perceptible changes in the femoral artery pressure. The systolic and the diastolic pressures above the occlusion increased only slightly and less than would be

expected from partial occlusion of such a large part of the circulatory system. In view of the absence of any decrease in cardiac output, one must conclude that a general vasodilatation occurred in the nonobstructed area.^{10, 1}

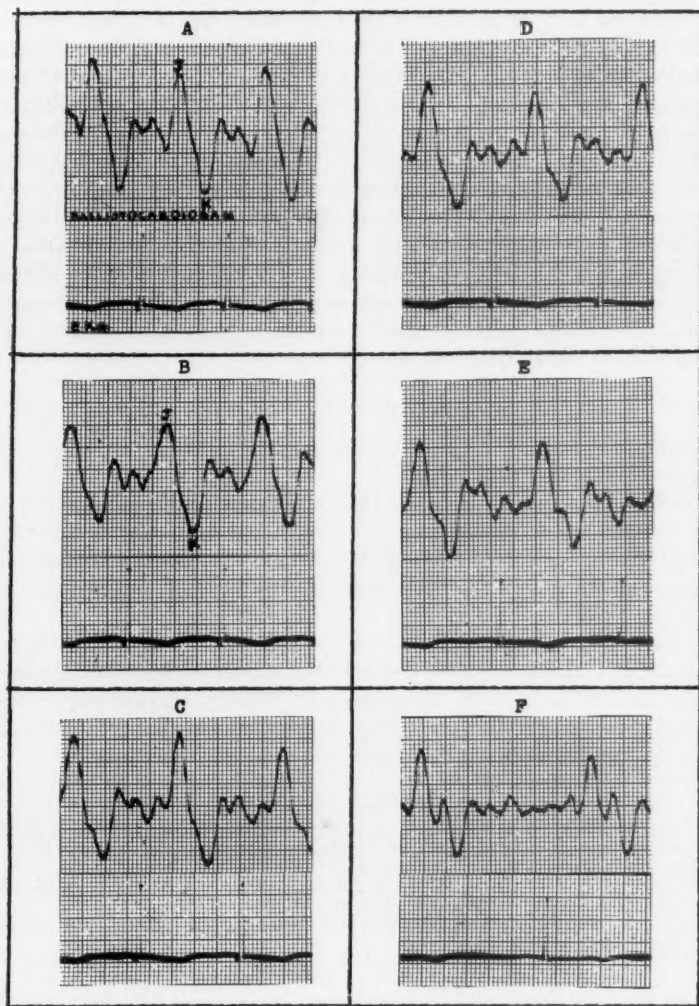


FIG. 4. Effects of progressive obstruction of the thoracic aorta on the contour of the ballistocardiogram. Segment A, control with no obstruction. Segments B, C, D, E, and F show the effects of progressive obstruction.

The behaviour of the heart is in accordance with Starling's Law.^{17, 14, 15} With 60 to 80 per cent obstruction of the lumen of the aorta, a small increase in the stroke volume was observed, and with further obstruction a rapid failure of the

heart was produced. The heart rate decreased with increasing pressure in the aortic arch and the carotid sinus. This decrease in heart rate is mainly mediated through the depressor nerve.

It appears therefore that the heart, at least in the dog, tolerates for a matter of hours, occlusions up to 80 per cent of the descending aorta. A greater obstruction will lead to a rapid left heart failure as was also shown by Hardin and Schafer.¹¹ In table I we observe that the acute failure of the heart is demonstrated by a sudden diminished cardiac output and stroke volume with 95 per cent obstruction.

In aortic coarctations in human beings, abnormalities in the ballistocardiogram have been reported repeatedly,^{13, 18, 3, 4} especially the absence of the K wave. The ballistocardiogram of the dog cannot be completely compared with the ballistocardiogram in human beings but the ballistocardiographic changes, as shown in figure 4, clearly indicate the influence of aortic obstruction upon the ballistocardiogram. The originally smooth down stroke, corresponding with the JK wave of the human ballistocardiogram, undergoes progressive changes with increasing obstruction of the thoracic aorta and finally a new wave (fig 4F) emerges between the J and the K waves.

SUMMARY AND CONCLUSIONS

A method was developed which permits the production of acute aortic occlusion in the closed chest of the dog.

Cardiac output was studied during the acute partial and complete obstruction (95 per cent) of the descending aorta in 4 dogs. The dogs tolerated obstruction up to 80 per cent for a few hours; further obstruction caused heart failure. The hemodynamic changes in the open chest are similar to those observed in the closed chest.

Ballistocardiographic changes were studied in 10 dogs with various degrees of obstruction. In such experiments, the interval between the J and the K wave was influenced in a definite way by the appearance of a new upward wave which occurred between J and K with increasing obstruction. The changes observed were roughly proportional to the degree of occlusions of the aortic lumen.

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OPEN METHOD OF BURN TREATMENT AND USE OF SKELETAL TRACTION

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Since the publication of his work on the exposure treatment of burns by Wallace⁴ in 1948, many clinics and medical centers have been evaluating this method of treatment. Blocker¹ has reported a very extensive series of patients treated without occlusive dressings with good results. He states, "We were surprised to discover that in spite of our disregard of aseptic precautions none of the patients developed the foul-smelling surface suppuration and general sepsis which we had come to believe was an inescapable phase in the course of recovery from major thickness burns." He found that the number of days during which the patient was febrile was less in patients treated by the exposure method than in patients treated by the occlusive dressing method. The number of days of hospitalization and the number of transfusions required were *materially reduced*.

Aims of the Exposure Method. The aims of the exposure method of treating burns as they were set forth by Kyle and Wallace² are as follows:

1. To produce an environment unfavorable to the growth and multiplication of bacteria by:
 - (a) the production of a dry surface
 - (b) exposure to light
 - (c) the reduction of the temperature of the surface to below that of the body.
2. To avoid antiseptics which cause further injury to tissue cells.
3. To provide rest of the affected part by immobilization.
4. To limit edema, where possible, by elevation.
5. To render nursing care simple in areas where dressings would otherwise be continually contaminated e.g. buttocks, thighs, perineum and face.

In the past 27 months we have treated 426 burned patients at the John Gaston Hospital. The vast majority of these patients were treated by the exposure method. Only those patients whose burns were not adaptable to the exposure method, such as burns of the hands and some circumferential burns of the extremities, were treated by the closed method.

Clinical Procedure. The procedure that is now followed at the John Gaston Hospital in treating patients by the exposure method is as follows: on admission to the hospital, attention is first directed toward the restoration of fluid and electrolyte balance. This phase of the treatment of burns must take precedence over any form of local treatment. The systolic blood pressure, the hematocrit, and the urinary output are used as indices as to the amounts of blood and elec-

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trolytes needed. At the present time blood rather than plasma is being used initially.

As soon as measures to restore the fluid and electrolyte balance are being carried out and the patient is out of shock, the burned areas are gently cleansed of gross dirt and soot with physiologic sodium chloride solution or a neutral detergent. Then the blisters and loose epidermis are removed. We believe that the more thoroughly the burned area is debrided on admission, the cleaner and more pliable will be the resulting eschar. Figure 1a shows a patient whose burned area was thoroughly debrided initially. Contrast this smooth, clean eschar with that formed upon the patient in figure 1b, whose burn was not completely debrided on admission. The brittle eschars on the poorly debrided patients crack more



FIG. 1a. Patient with second and third degree burns on the ninth day after being burned. This patient had thorough debridement of burned area on admission to the hospital.

readily and admit more infection than the clean, pliable eschars of the other patients.

After the debridement the patient must be placed on a sterile sheet in such a position that the burned area will be exposed to the air; will not touch the sheets; and in the case of an extremity, will be immobilized. It often requires some ingenuity to achieve these objectives in extensive burns. In those patients who are burned on only one side of the trunk or extremities, simple bed rest on the unaffected side with care to prevent prolonged pressure on the bony prominences is all that is necessary. The covers are kept off the burned area by a cradle over the patient. This is not a heat cradle and no light bulbs should be placed inside it. One of the objectives in the open method is to keep the surface temperature low. In circular burns of the trunk or extremities exposure of the burned areas is often difficult. For certain of these we have used skeletal traction.

In from 48 to 72 hours after the burned area is exposed to the air, an eschar has formed which is impervious to bacteria and which also prevents the further loss of fluid. In from 10 to 21 days, depending upon the depth and location of the burn, this eschar is removed in the operating room under anesthesia and in most instances immediate grafting is possible. If it is not practical to remove the eschar in the operating room under anesthesia, it may be removed by application of continuous moist dressings. This, of course, prolongs the period of hospitalization. During the period when the burned area is covered with the eschar it is necessary to do fractional debridement at the curled up edges and where cracks occur. If the edges of these cracks are not trimmed to produce wide drainage, infection will spread beneath the eschar.

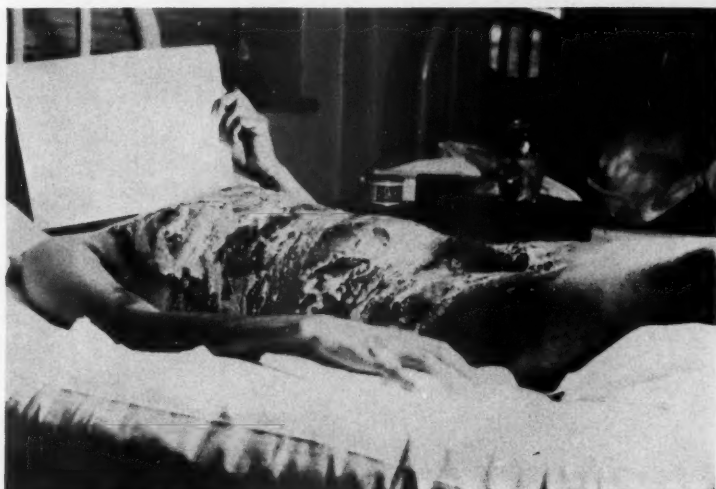


FIG. 1b. Patient with second and third degree burns on the eleventh day after being burned. This patient had incomplete debridement of the burned area.

After the patient's wounds are grafted, the grafts are covered with fine mesh gauze or silk impregnated with some bland ointment, and a pressure dressing is applied. The further treatment then is the same as though the patients had been treated by the occlusive dressing method from the beginning. The dressing is carefully changed in five days and as needed thereafter. If it has been impossible to completely cover the area of total skin loss at the first operation, operations are repeated at weekly intervals until all areas are covered. Attention must be directed toward the maintenance of protein and hemoglobin levels during the period between operations.

Use of Skeletal Traction. Although Wallace⁴ reports that the use of a pin through the calcaneus may be useful as a means of positioning patients with circumferential burns of the trunk or lower extremity—and shows a photograph of such a patient—this method of positioning patients has received very little at-

tention and we are not aware of any other reports of its having been used. It now is our belief that this method should be used only in selected cases, when the



FIG. 2a

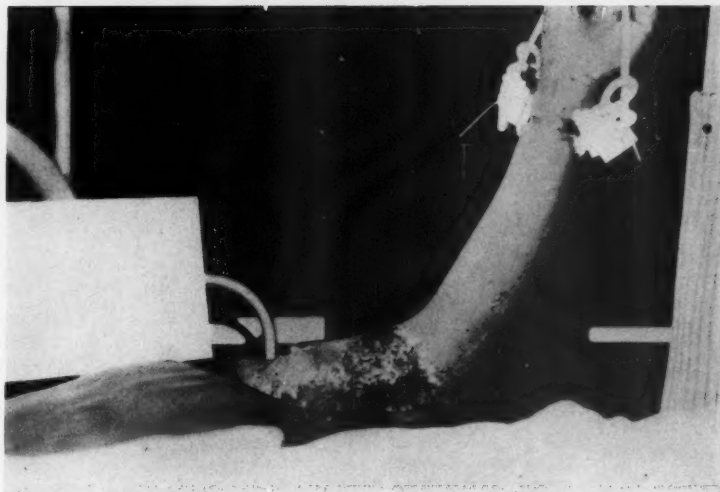


FIG. 2b

FIGS. 2a and 2b. Patients with a small area of third degree burn. These patients were treated very satisfactorily by the exposure method with skeletal traction but could have been treated by the occlusive dressing method with less hospitalization.

seriousness of the burn justifies the risk of osteomyelitis incident to skeletal traction. Figures 2a, 2b, 3, 4, and 5 show patients in whom this skeletal traction



FIG. 3. I. S., CF, aged 5. This patient was admitted to the John Gaston Hospital Feb. 10, 1951, with an estimated 70 per cent of the body surface affected with second and third degree burns. This child was treated with the occlusive dressing method for 11 days, during which time the temperature rose each day to 103 F. On the twelfth day the trunk was exposed. Within 24 hours the temperature came down to 100 F. and did not again rise. Her wounds were grafted first with homografts which remained viable for three weeks. These were then replaced with autografts in multiple grafting operations.



FIG. 4. A. T., CF, aged 7. This patient was admitted to John Gaston Hospital April 4, 1953, with an estimated 25 per cent of the body surface covered with second and third degree burns. Here the occlusive dressings again were applied for the first 12 days. Because of continued fever of 102 to 103 F., Kirschner wires were placed through the femurs and the burned areas exposed. The temperature promptly came down to 100 F. Twelve days later the eschar was removed in the operating room under anesthesia. The areas were not clean enough to graft at that time. The patient is now in her third day since the removal of the eschar and her wounds will be grafted in the next day or two. For convenience in grafting and to simplify the nursing care, she has been left suspended, but the Kirschner wires will be removed when her wounds are grafted the first time. The feet have been properly supported in position of function since the photograph was made.

was utilized. Patients such as those pictured in figures 2a and 2b do not have burns of sufficient extent to justify this risk. They came in for treatment at a time when the exposure method was being used on all patients in order to determine its usefulness. They could have been treated by the occlusive dressings and then would have been able to remain at home until their wounds were ready for grafting. We believe that the use of the exposure method of treating burns was the most effective way of treating the severely burned children pictured in figures 3, 4, and 5, and that only by use of skeletal traction was this possible. In all, some 20 patients have had either their trunks or extremities elevated by skeletal trac-



FIG. 5. P. M. O., CF, aged 5. This child was admitted to the John Gaston Hospital on April 18, 1953, with an estimated 60 per cent of the body surface covered with second and third degree burns. She was not suspended until the seventh day after admission. Since being exposed to the air there has been no dramatic change in the temperature, but the patient appears less toxic and much more comfortable. On the eleventh day after being suspended, the eschar was removed under anesthesia. The trunk was again exposed to the air since it was thought that the wounds on her arms and hands should be grafted first and since we believe that it is much easier to keep an area clean if it is dry than when it is dressed and wet. At the present time the second eschar—a clean pliable one—has formed over the trunk and the hands are receiving moist dressings, preparing them for grafting. The feet have been properly supported in the position of function since the photograph was made.

tion. We have not encountered a single case of osteomyelitis. The Kirschner wires have been placed through the calcaneus bone on some patients to elevate the lower extremity. When this is done the foot must be maintained in functional position or a foot drop will result. The patients who have suspension through the calcaneus complain of pain in the knee unless additional support can be placed to allow the knee to remain flexed. The joints and parts distal to the point of transfixion must be supported in all cases. In 1 case Steinmann pins were placed through the femurs just above the condyle and the trunk was elevated. This proved to be a heavier wire than was necessary, although this was an adult

patient. An area of necrosis of the soft tissue about 1 cm. in diameter developed around the pin. Although we feared osteomyelitis would develop, none was apparent clinically or roentgenologically.

There appear to be certain advantages in the use of the exposure method in the treatment of burns. Some of these are:

1. The patient is free of the odor that frequently accompanies the use of the pressure dressing method. For this reason, his morale is higher and his appetite is better than in the patient treated with the closed method.

2. There is less protein and blood loss by the exposure method. The eschar serves as a seal to prevent the loss of protein, and the bleeding which almost invariably accompanies the changing of dressings is not encountered.

3. The number of dressings necessary in treating a third degree burn is reduced by about one-half. In the case of a private patient this results in a substantial saving to the patient. In an institution where a limited number of professional personnel is caring for the burns, this relieves the personnel of a burdensome, routine task, and they can devote more time and energy to dressing the patients whose wounds have been grafted and to the maintenance of the nutritional status of all the patients.

4. Fewer second degree burns are converted to third degree burns by being covered by the natural eschar than by being covered by an irritating chemical or bathed in pus.

SUMMARY

The aims of the exposure method of treating burns have been reviewed.

The procedure used in the application of the exposure method by the author has been given.

A method of exposing extensive circumferential burns of the trunk and extremities by skeletal traction is presented.

Some of the advantages of the exposure method of treating burns are given.

Addendum: The patients illustrated in Figures 4 and 5 have been completely grafted and have been discharged from the hospital since the manuscript was submitted.

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PRIMARY CARCINOMA OF THE APPENDIX

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Surgical literature contains several reports concerning tumors of the vermiform appendix,^{1, 3, 4, 5, 6, 8} but until the work of Uihlein and McDonald⁷ little interest was evinced regarding these tumors. The surgeon in seeking a workable classification for tumors of the appendix should welcome their grouping. They are: first, the carcinoid type (fig. 1); second, cystic or mucocele type the precursor of pseudomyxoma peritonei (fig. 2); and third, the colonic or adenocarcinoma which is the true primary carcinoma of the appendix. Failure of the surgeon to differentiate the foregoing may prove disastrous.

The carcinoid type is usually found at or near the tip of the appendix. In the gross it is yellowish, solid and secretes no mucus. Metastasis to regional nodes may occur in less than 1 per cent of this type.

Cystic lesions of the appendix present an entirely different picture. The cystic type has an affinity for the base and tip, more often selecting the base with a resultant occlusion of the lumen. These form the basis for a mucocele which may perforate leading to metastasis in kind, pseudomyxoma peritonei. The cyst may obtain enormous size without rupture, eventuating in an intestinal obstruction at the ileocecal orifice by mechanical blocking; such a condition was reported by the essayist in 1934.² Large quantities of mucus is usually secreted; the serosa is pale and blanched unless an acute inflammatory process has supervened; a sausage-like feel is at times imparted to the examining fingers.

The colonic or adenocarcinoma type is most frequently seen in the body or base of the appendix. Those found at the base usually represent an invasion of adenocarcinoma by direct extension from the cecum, obviously not constituting a primary carcinoma of the epithelial elements of the appendix. A rather characteristic grayish color is noted with a polypoid appearance and frequently ulceration. At times the carcinoma arises on the base of an adenomatous polyp in the lumen of the appendix involving a limited portion. A primary carcinoma of the vermiform appendix may secrete variable quantities of mucus and metastases in varying degrees may involve the lymph nodes and the liver by the same distribution that one finds in malignancy of the right colon.

The microscopic structures of the three types present very definite patterns which the pathologist has little difficulty in recognizing and, therefore, may be of inestimable value to the surgeon. Examination of a microscopic section should be made at the time of operation, if doubt exists as to the nature of the lesion.

Should the gross or the microscopic examination reveal a primary carcinoma in the appendix, the surgeon from necessity must adopt an aggressive surgical procedure, such as radical resection of the terminal ileum and right colon with

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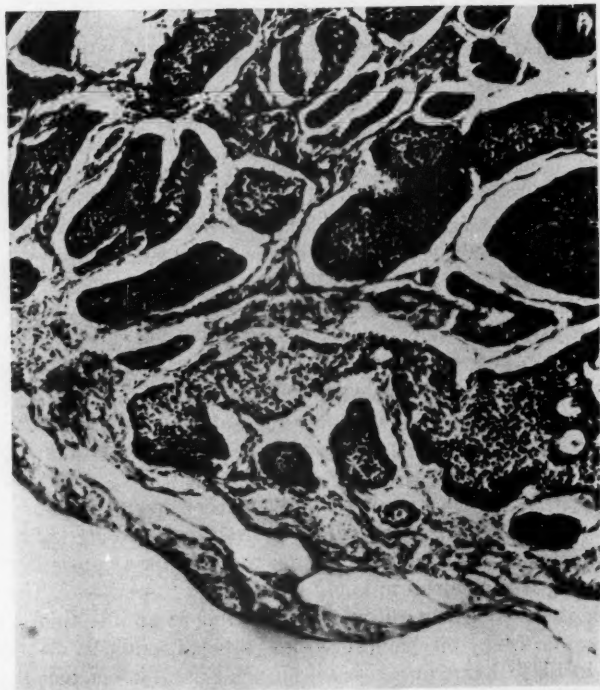


FIG. 1. Carcinoid of appendix

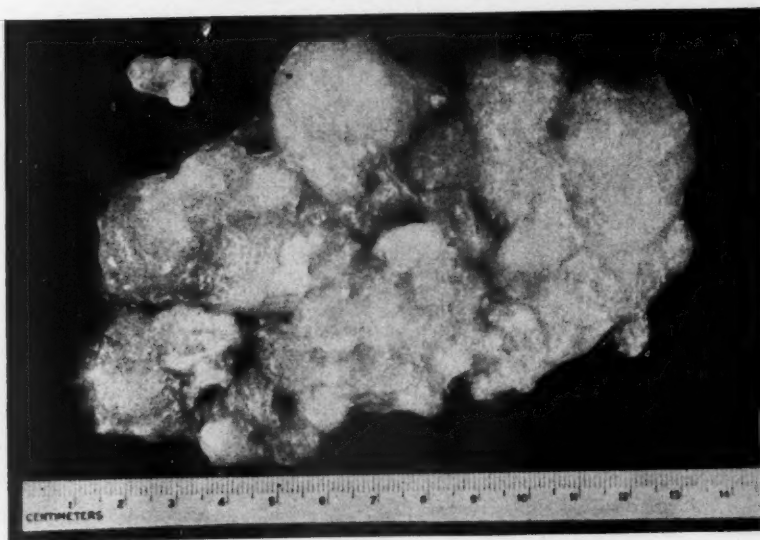


FIG. 2. Mucocoele of appendix with pseudomyxoma peritonei

an ileotransversostomy. A more simple operation for the nonmalignant types may be used, such as simple appendectomy, which on occasion must be extended to include a cecectomy.

The definite confusion and paucity of reports existing in the past concerning the diagnosis and treatment of tumors of the appendix, especially those pertaining to primary carcinoma, encouraged the following case report.

CASE REPORT

Mrs. J. Y., aged 67, was admitted to the Kentucky Baptist Hospital on Feb. 4, 1951 complaining of pain in the lower right quadrant of the abdomen accompanied by nausea and vomiting. Two days before her admission pain began abruptly in her right lower abdomen



FIG. 3. Primary adenocarcinoma of appendix with terminal ileum and ascending colon

and within three hours nausea and vomiting ensued. For six months she had experienced recurrent episodes of mild pain in the lower right abdomen which had not been followed by nausea and vomiting. Some five days previous to her present illness a mild diarrhea occurred, but no blood was visible and the diarrhea disappeared within 36 hours. She had at no time seen any change in the color of her stools; her bowel habits had not deviated from her regular pattern over the years. Her past and family histories failed to reveal any positive findings which might be correlated with her present illness.

The abdomen was moderately distended; increased muscle rigidity was evident in the lower right quadrant; a round circumscribed tender mass was palpated in the right lower quadrant. Pain and rebound tenderness were very definite. A rectal examination with the scope produced no positive findings.

The temperature was 100 F.; pulse 90; respirations 20; systolic blood pressure 200 and diastolic 90. The red cell count was 3,620,000 per cu. mm., color index .92, hemoglobin 80 per cent, white blood cells 10,500 per cu. mm. with 90 per cent of polymorphonuclears. The urine showed a slight trace of albumin.

Acute appendicitis was recorded as a diagnosis. Under spinal and sodium pentothal anesthesia, the abdomen was opened through a right pararectus incision. The appendix presented a lobulated tumor measuring 6 by 3 by 4 cm. The surface of the mass was smooth except in one portion which was thickened and cystic. The base was acutely inflamed and the vessels very much engorged. The tumor resembled a white solid ovary. No enlarged nodes could be palpated in the ileocecal region or the mesentery of the ileum. The liver was palpated and no metastatic nodules were found.

From the gross picture it was deemed wise to use an aggressive surgical procedure. The terminal ileum, the cecum and the ascending colon were resected (fig. 3) and an end to side ileotransversostomy was done. The patient made an uneventful recovery except for some slight distention persisting three days postoperatively, which was relieved by the nasogastric tube and suction.

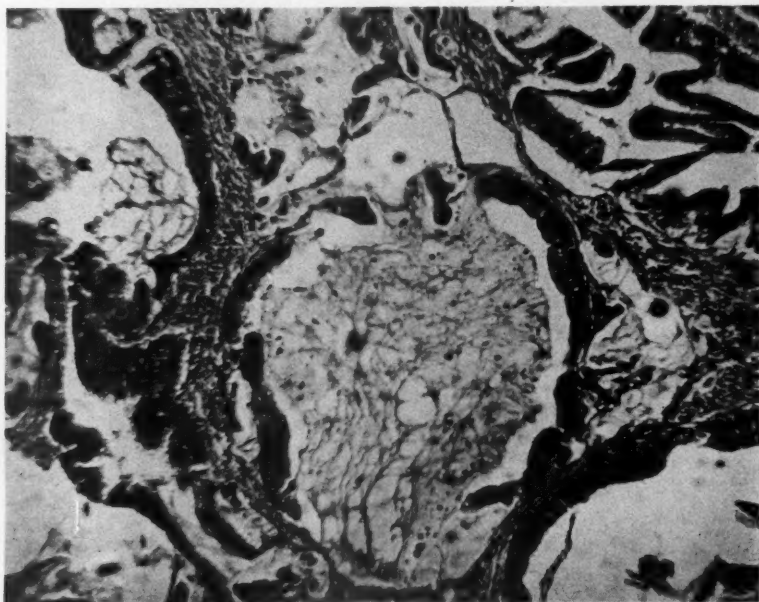


FIG. 4. Primary mucinous adenocarcinoma of the appendix

The pathologic report was as follows:

Gross. The specimen consists of the terminal ileum, cecum and of the ascending colon. The terminal ileum measures 11 cm. the cecum and ascending colon measures 14 cm. in length. Attached to the lower part of the cecum, apparently at the site of the appendix, there is a lobulated tumor measuring 6 by 3 by 4 cm. The surface of the mass is smooth and one portion is thickened and cystic. The cyst wall measures approximately 1 mm. in thickness. The lumen of the cyst is filled with a grumous reddish yellow and caseous material containing cholesterol crystals. The lumen of the ileum shows no evidence of invasion. The end of the cecal pouch contains a reddish papillary fungating mass projecting from what appears to be the usual site of the appendiceal orifice. This is intimately connected with the adjacent tumor which appears to infiltrate at this point. Multiple sections show tumor tissue composed of variously fibrous mucinous hemorrhagic and necrotic material.

Microscopic Description. Sections from the base of the appendix and cecum show normal

appendiceal mucosa containing lymphoid follicles continuous with a neoplastic epithelium closely resembling that lining the appendix and appendiceal glands, but containing larger, more hyperchromatic and pleomorphic nuclei, with large nucleoli. Beneath the appendiceal mucosa in the submucosa there are numerous bizarre neoplastic glands containing mucus. Projecting into the base of the cecum is a similar neoplastic tumor showing large areas filled with mucus containing a dense collagenous stroma and fragments of mucus-producing neoplastic glandular epithelium with a tendency to papillary formation. Sections through the cystic structure containing yellow material shows a thick fibrous capsule with a content of necrotic material containing numerous cholesterol clefts.

Diagnosis. Mucinous adenocarcinoma of the appendix (fig. 4).

CONCLUSIONS

A brief resume of three different types of tumors of the appendix is presented. The report of a primary adenocarcinoma of the appendix is recorded.

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EDITORIAL

ON THE POSSIBILITY OF ERADICATING BREAST CANCER BY OPERATION

The radical removal of metastasizing cancer was first attempted on cancer of the breast. It was based on two assumptions: (1) that cancer spreads entirely, or nearly so, by way of lymphatics, and (2) that this spread is by an unbroken growth within lymph vessels, so that the cancer and all its ramifications form a continuous whole. If these assumptions be true, then a cancer can be removed by cutting beyond all parts of it through healthy tissue. This is the theory of block dissection, which was advanced over 50 years ago by Halsted and Handley and was the theoretical justification for the operative treatment which they advocated for cancer of the breast. It was immediately applied to the treatment of cancer anywhere in the body and it still dominates that treatment, although certain writers have modified it of late. They have done so because, apparently, they find it hard to believe that a true block removal of cancer from many of its locations can be accomplished. They hold fast to the belief that cancer spreads chiefly, if not entirely, by way of lymphatics, but maintain that this spread occurs, not by a continuous growth of cancer within these vessels, but by emboli of cancer cells which travel along them to lymph nodes. This belief supports a faith that cancer can be eradicated by removal of the primary growth and all secondary growths in lymph nodes. Pursuant to it, many laborious studies have been made on the location of lymph nodes which may receive emboli from cancers situated in various places, and these studies have greatly increased the extent of operations for cancer.

It is true that emboli of cancer cells can travel along lymph vessels to lymph nodes, but it is also true that cancer is present for unknown distances in lymph vessels around cancerous nodes. Removal of the cancerous nodes is of no avail if these cancer-filled lymph vessels are not removed also, and we have good reason to doubt that this often can be done. My skepticism about this matter was increased by observations which my associate, Dr. C. G. Culbertson, made, with a refined technic, on axillary fat removed by the radical operation for breast cancer. The specimens he studied all has been pronounced free of cancer when examined while fresh by inspection and palpation; yet, in many of them, he demonstrated cancer in lymph vessels and in minute lymph nodes. The possibility of removing all this widespread and unseen cancer by any dissection, no matter how long and painstaking it may be, is remote.

A corollary of the theory that cancer spreads almost entirely by way of lymph vessels is that the earlier operation is done in the course of the disease, the better the prognosis. This is the fundamental doctrine on which present plans to control cancer are based, and it requires great hardihood to question its validity. Many careful students of breast cancer do so, however, because no one has shown conclusively that the results of early operation are better—within reasonable limits—than those of later operation. Statistically, they actually seem to be worse.

This may be because rapidly growing cancers, which kill sooner, are likely to be discovered sooner and operated upon sooner than cancers of slower growth. Early operation may be better for the individual patient than later operation, but not so much better as is commonly taught.

Failure to distinguish the two meanings of the word early, when it qualifies operation, diminishes the value of most statistical studies on the results of operation for cancer. Early may mean either of short duration, or of limited extent. A growth of short duration may have a wide extent, and vice versa. By early operation, writers mean operation done soon after the patient discovers the growth. Strictly speaking, the duration of a cancer at operation is the duration between then and when it started in a cell or group of cells. We know next to nothing about the length of this period, but the available evidence indicates that for many cancers it is very long. The prostates of about 25 out of every 100 men over 50 years of age are known to contain minute, dormant cancers. Perhaps the breast often contains cancers of this kind. Dr. C. G. Culbertson has, in fact, demonstrated cancers of microscopic size in a number of breasts removed for benign lesions. A disconcerting fact is that these cancers—too small to be felt—may have distant metastases.

Batson has made it impossible to believe any longer that breast cancer spreads rarely or never by way of blood vessels. He has demonstrated a primitive, capacious system of veins without valves which extends along the spine from skull to coccyx and has numerous anastomoses with veins in the structures adjacent to the spine. He could fill this system with a radiopaque solution injected either through a superficial vein of the breast or the dorsal vein of the penis. He proved that cancer cells can reach the spine, ribs, brain, pleura, etc., by way of these spinal veins without passing through a lung; also, that the locations of metastases of breast and of prostatic cancer in bones are the same as these reached by his injections. He showed that coughing, straining, and bodily movements may propel particulate matter into and along these spinal veins. His findings explain the presence of metastatic breast cancer in eye, brain, and in the proximal ends of humerus and femur. Handley taught that fragments of breast cancer often travel to the lungs in the blood, but seldom survive there; that successful invasion of the chest by this growth is almost always by way of lymphatics which conduct it to the pleura. The observations of roentgenologists of metastatic cancer in the lung, when none of it can be seen in the pleura, shows that this dictum is not entirely true. For all we know, cancer cells may sometimes pass clear through lung capillaries into the left auricle of the heart.

The extremely variable course of breast cancer, treated or untreated, makes appraisal of the benefits of operating for it difficult and uncertain. The following facts make this plain:

1. The duration of life without operation, following discovery of a breast cancer, ranges from 1 to over 25 years. The statement, often made, that the average length of this period is from three to four years, is of statistical value only. The total life of the cancer, from its inception until it kills its host, is unknown.
2. The rate of growth of an individual cancer may be very slow at one time,

and very fast at another. This is especially true of its metastases. These may be dormant and unknown for decades.

3. Breast cancer kills, not by its local, but by its metastatic growth. A crucial and unanswered question is what, if anything, operation does to prevent metastasis.

4. Minute metastases are often widespread in axillary fat which will be pronounced free of cancer, unless it be examined by a special and laborious technic. This fact is important, because of the great prognostic significance attached to the absence of cancer in the axilla.

The foregoing discussion explains the present confusion of thought on what is the proper operation for breast cancer. Some advocate simple mastectomy; others, extension of the operation into the neck and chest. Although we can no longer accept the theories on which the Halsted operation was based, we believe that experience has proved it to be the operation of choice for most cases of breast cancer. It gives a clinical cure—lasting five years or longer in a considerable number of cases—and it permits perhaps 85 per cent of all patients to die of internal metastases or intercurrent disease, without the affliction of an external growth. It furthermore causes—in most cases—no serious deformity or disability. Extension of the operation into the neck or chest—in the opinion of the writer—is worse than useless. We can no longer be sure that any patient is completely free of breast cancer; for it may be quiescent for many years.

The first thing nature had to do when it created a multicellular organism was to regulate the division of its individual cells according to the needs of the organism as a whole. How nature does this is perhaps the most important secret in biology. This tissue resistance to neoplastic growth is usually very powerful; and I believe it explains the anomalous and unpredictable behavior of breast cancer. I believe also that we are deeply indebted to it for whatever good results we obtain from operations for this disease; also that these operations—if improperly done, or unduly extensive and prolonged—may decrease or destroy this tissue resistance.

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BOOK REVIEWS

The editors of THE AMERICAN SURGEON will at all times welcome new books in the field of surgery and will acknowledge their receipt in these pages. The editors do not, however, agree to review all books that have been submitted without solicitation.

Surgery of the Pancreas. By RICHARD B. CATTELL, M.D., Surgeon, The Lahey Clinic, New England Baptist Hospital, New England Deaconess Hospital. And KENNETH W. WARREN, M.D., Surgeon, The Lahey Clinic, New England Baptist Hospital, New England Deaconess Hospital. W. B. Saunders Company, Philadelphia and London, 1953. 374 Pages.

The authors state that this book is based on experiences with over 1000 patients with surgical diseases of the pancreas treated at the Lahey Clinic. In addition to a study of the material in the Lahey Clinic an adequate review of the literature has been made and the references are appended at the end of each chapter.

The first chapter is devoted to the anatomy and physiology of the pancreas. Succeeding chapters discuss congenital malformations of the pancreas, acute pancreatitis, chronic relapsing pancreatitis, pancreatic cysts, pancreatic injuries, islet cell adenomas and hyperinsulinism, carcinoma of the pancreas and periampullary area, and total pancreatectomy.

In the chapter on "Acute Pancreatitis" there is a short historical note followed by a thorough review of the etiology, pathology, symptomatology, methods of examination and medical and surgical treatment. That difficult subject, Chronic Relapsing Pancreatitis, is very well presented. The modern treatment of pancreatic cysts, the medical and surgical aspects of hyperinsulinism, and the management of pancreatic injuries, are all ably presented.

The critical study of carcinoma of the pancreas and periampullary area, with the authors' results of treatment, are to be praised. Five of 32 patients (16 per cent) who had pancreatoduodenectomies for carcinoma of the head of the pancreas, ampulla of Vater, duodenum and distal end of the common duct have survived from five to nine years.

The text is adequately illustrated with good drawings, roentgenograms and charts.

This book is not a monograph for surgeons only, but would be of great value to any physician who is called upon to diagnose and treat diseases of the pancreas.

THOMAS G. ORR, M.D.

Surgery of the Oesophagus. By R. H. FRANKLIN, M.D., D.S.F.R.C.S. Senior Lecturer and Surgeon, Post Graduate Medical School of London, Consulting Surgeon Kingston Hospital, Late Hunterian Professor, Royal College of Surgeons, London, England, The Williams & Wilkins Co., Baltimore, Maryland, 219 pages, four color plates. \$8.50.

Franklin's "Surgery of the Oesophagus" is a very good book which blends the most up to date considerations of the entire esophagus, with a colorful historical background of the subject. It clearly emphasizes the fact that judicious management of esophageal disease requires an appreciation that the organ should be treated as a whole, not compartmentalized. This suggests, at first, great versatility by general surgeons familiar with endoscopy and experienced in the neck, thorax and abdomen of adults and infants. At the same time, he points out, similar ends are obtained by cooperation with the endoscopist, radiologist and specialist surgeons.

The book is relatively short, is clearly and interestingly written, and well organized. It discusses the benign and malignant diseases of the esophagus, congenital and acquired. It is illustrated by a few well chosen case histories, roentgenologic reproductions, drawings and photographs. Although there naturally are differences of opinion concerning the minor facets of the problems presented, the advantages and disadvantages of varying views are presented fairly and simply.

General principles of the physiology, embryology and pathology of each esophageal condition are excellently presented in short order. Good treatment of many specific details of management and technic are outlined. This book should appeal to every surgeon dealing with any part of the esophagus.

STANLEY FRIESEN, M.D.

The Surgery of Infancy and Childhood: Its Principles and Techniques. By ROBERT E. GROSS, M.D., D.Sc., William E. Ladd Professor of Children's Surgery, The Harvard Medical School, Chief of Surgical Service, The Children's Hospital, Boston. W. B. Saunders Company, Philadelphia and London, 1953.

This book of 1000 pages is a product of the author's experience with a very active surgical service at the Boston Children's Hospital. In 1950 there were 5396 operations in all departments of surgery of which 2447 were in the division of general surgery.

Each subject in the book is well presented and summarized with a statistical study of the number of patients treated with the results of treatment.

In this review it is obvious that the surgery of infancy and childhood presents many problems that differ from those of adult surgery. The author correctly states that "at the operating table there is no opportunity to read or consult about the problem at hand, and not infrequently procedures may be carried out which are far from optimum in giving a child the best chance of survival." This makes a good book on surgery of infancy and childhood a necessity for general surgeons.

The chapters on "Preoperative and Postoperative Care" and "Anesthesia for Pediatric Surgery" are particularly noteworthy. In reviewing the other chapters one is impressed with the importance of congenital anomalies in the field of pediatric surgery. The surgery of congenital anomalies is adequately covered in this book.

The drawings, photographs, roentgenograms and charts well illustrate the subject matter. Pertinent references to surgical literature of the surgery of childhood appear at the end of each chapter.

Surgeons, pediatricians, residents and interns all need this book for reference. It is the opinion of the reviewer that this book by Dr. Gross deserves the highest praise.

THOMAS G. ORR, M.D.

A Short Practice of Surgery. By HAMILTON BAILEY, F.R.C.S. (Eng.), F.A.C.S., F.I.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, London; Senior Surgeon, St. Vincent's Clinic and the Italian Hospital; Formerly Externa Examiner in Surgery, University of Bristol and R. J. McNeill Love, M.S. (Lond.) F.R.C.S. (Eng.), F.A.C.S., F.I.C.S., Surgeon, Royal Northern Mildmay Mission, and Metropolitan Hospitals, Consulting Surgeon, City of London Maternity Hospital; Consulting Surgeon, Potter's Bar Hospital; Associate for General Surgery, West End Hospital for Nervous Diseases; Member of Council and Court of Examiners, Erasmus Wilson Demonstrator, and Hunterian Professor, Royal College of Surgeons, with Pathological Illustrations by L. C. D. Hermitte, M.D., Ch. B. (Edin.), Pathologist, Royal Infirmary, Sheffield. Ninth Edition (65th thousand) Baltimore, Md. The Williams & Wilkins Company, 1953. \$12.50.

For beginning students in general surgery or those who desire an orderly review, "A Short Practice of Surgery" will prove of utmost value. In its 1254 pages it discusses in a concise fashion most of the diseases usually included in general surgery, urology, and orthopedics. Particular attention is directed to the etiology, regional anatomy, pathology, the history and examination of the patient, and, refraining from technical operative details, the treatment of these conditions. The illustrations are numerous (1234 figures), of good quality, and enhance the educational facility of the book considerably. An unusual feature is an identifying footnote about each person mentioned in the text, whether eponymically or otherwise.

In general the discussion about any particular subject is meager. It appears as though an attempt has been made to enumerate as many conditions as possible, even though some

n- mentioned are extremely rare, rather than to present a more comprehensive detailed study
of fewer disease states. The text is given as the authors' personal conclusions, no bibli-
ography being listed, and quotations being infrequent. The style, as in most English med-
ical writings, is lucid, direct, and well-organized.

D. The book has been revised considerably and brought up-to-date from its previous edi-
tions. That a ninth edition is warranted is ample testimony of its general excellence. It
deserves a prominent place in every general surgical library and should be welcomed by all
who are interested in surgery, but who may not as yet have become acquainted with this
text.

C. F. KITTLE, M.D.

